UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

BTG INTERNATIONAL LIMITED, et al., Plaintiffs, **v.** **AMNEAL PHARMACEUTICALS LLC, et al.** Defendants.	Civ. No. 15-cv-5909 (KM)(JBC)
BTG INTERNATIONAL LIMITED, et al., Plaintiffs, **v.** **AMERIGEN PHARMACEUTICALS, INC., and AMERIGEN PHARMACEUTICALS LTD.,** Defendants.	Civ. No. 16-cv-2449 (KM)(JBC)
BTG INTERNATIONAL LIMITED, et al., Plaintiffs, **v.** **TEVA PHARMACEUTICALS USA, INC.,** Defendant.	Civ. No. 17-cv-6435 (KM)(JBC) **CONSOLIDATED OPINION**

KEVIN MCNULTY, U.S.D.J.:

These are consolidated Hatch-Waxman actions for infringement of United States Patent No. 8,822,438 ("the '438 patent") brought by Janssen Biotech, Inc.; Janssen Oncology, Inc.; Janssen Research & Development, LLC (collectively, "Janssen"); and BTG International Ltd. ("BTG"). Janssen and BTG co-own the '438 patent. The '438 patent contains twenty claims covering methods for the treatment of prostate cancer by administering various dosages

of abiraterone acetate and prednisone in combination. Patent exclusivity for these medications individually is not at issue.

The defendants are Amerigen Pharmaceuticals, Inc.; Amerigen Pharmaceuticals Ltd. (collectively, "Amerigen"); Amneal Pharmaceuticals LLC; Amneal Pharmaceuticals of New York, LLC (collectively, "Amneal"); Dr. Reddy's Laboratories, Inc.; Dr. Reddy's Laboratories, Ltd. (collectively "DRL"); Mylan Pharmaceuticals Inc.; Mylan, Inc. (collectively, "Mylan"); Teva Pharmaceuticals USA, Inc. ("Teva"); West-Ward Pharmaceutical Corporation, and Hikma Pharmaceuticals, LLC ("West-Ward/Hikman"); Wockhardt Bio AG; Wockhardt USA LLC; and Wockhardt Ltd. (collectively, "Wockhardt"). The defendants are generic drug companies who seek to engage in the commercial manufacture, use, offer for sale, or sale of a generic version of the plaintiffs' branded drug, ZYTIGA®.

Plaintiffs allege infringement of claims 4, 8, 11, 19 and 20, all of which rely on claim 1 of the '438 patent, based on the defendants' filing of Abbreviated New Drug Applications ("ANDAs"). If defendants' ANDAs are approved, defendants will allegedly induce infringement of the asserted claims of the '438 patent under 35 U.S.C. § 271(b) and contribute to infringement of the asserted claims under 35 U.S.C. § 271(c). Defendants deny infringement and claim that the patent claims are invalid for obviousness and for lack of a written description.

On November 3, 2017, defendants moved for summary judgment as to the induced and contributory infringement claims. (DE 364). The Court held a hearing on that motion on February 9, 2018. Because it appeared that there were issues of fact to be tried in any event, and that the issues on summary judgment would subsumed in those to be tried, the motion was terminated without prejudice to reassertion of all contentions therein following trial. (DE 483).

Meanwhile, on January 17, 2018, the Patent Trial and Appeal Board ("PTAB"), in three inter partes proceedings, found the patent invalid. A motion for reconsideration remains pending.

The Court conducted a bench trial beginning on July 23, 2018 and concluding on August 2, 2018. The parties have submitted post-trial briefing, as well as proposed findings of fact and conclusions of law.

This Consolidated Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). The findings of fact are based on the Court's observations and credibility determinations of the witnesses who testified at trial and a thorough review of all the evidence.

Essentially, I rule as follows: Like the PTAB, I find that the '438 patent is invalid for obviousness. I find the patent's written description to be adequate, however. In the alternative, and to facilitate appellate review, I have ruled on the infringement issues that were tried. Assuming that the '438 patent is valid, I find based on the proposed generic labels that the ANDA defendants' marketing of abiraterone would infringe, on either an induced infringement or contributory infringement theory.

I. FINDINGS OF FACT[1]

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[1] I will cite to the record as follows:

DE __	=	Docket Entry in this action, Civ. No. 15-5909
DBr.	=	Defendants' Opening Post-Trial Brief (DE 533)
Def. Response	=	Defendants' Post-Trial Response Brief (DE 552)
DPF.	=	Defendants' Proposed Findings of Fact (DE 534)
DTX	=	Defendants' trial exhibits
JTX	=	Parties' joint trial exhibits
PTX	=	Plaintiffs' trial exhibits
PBr.	=	Plaintiffs' Opening Post-Trial Brief (DE 535)
PPF.	=	Plaintiffs' Proposed Findings of Fact (DE 549)
Pl. Response	=	Plaintiffs' Post-Trial Response Brief (DE 552)
1T	=	July 23, 2018 Bench Trial Transcript (DE 539)
2T	=	July 24, 2018 Bench Trial Transcript (DE 540)
3T	=	July 25, 2018 Bench Trial Transcript (DE 547)
4T	=	July 26, 2018 Bench Trial Transcript (DE 541)

A. Procedural Background

1. On July 31, 2015, plaintiffs filed a complaint for infringement of the '438 patent based on defendants' ANDA filings, which sought approval to market generic abiraterone acetate[2] 250 mg tablets. (Civil Action No. 15-5909, DE 1). Plaintiffs filed suit against the following ANDA defendants:

a. Actavis Laboratories FL, Inc., Actavis Pharma, Inc., and Actavis, Inc. ("Actavis"), related to ANDA No. 208274[3];

b. Amneal related to ANDA No. 208327;

c. Apotex Corp. and Apotex Inc. ("Apotex") related to ANDA No. 208453;

d. Citron Pharma LLC ("Citron") related to ANDA No. 208371[4];

e. DRL related to ANDA No. 208416;

f. Mylan related to ANDA No. 208446;

g. Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. ("Par") related to ANDA No. 208168;

h. Sun Pharmaceuticals Industries, Ltd. and Sun Pharmaceuticals Industries, Inc. ("Sun") related to ANDA No. 208440;

i. Teva and Teva Pharmaceuticals Industries Limited related to ANDA No. 208432;

j. West-Ward/Hikma, The Arab Pharmaceutical Manufacturing Co. and Hikma Pharmaceuticals, PLC, related to ANDA No. 208339; and

k. Wockhardt related to ANDA No. 208380.

5T	=	July 27, 2018 Bench Trial Transcript (DE 542)
6T	=	July 30, 2018 Bench Trial Transcript (DE 543)
7T	=	July 31, 2018 Bench Trial Transcript (DE 544)
8T	=	August 1, 2018 Bench Trial Transcript (DE 545)
9T	=	August 2, 2018 Bench Trial Transcript (DE 546)

[2] Unless otherwise specified, abiraterone and abiraterone acetate, its prodrug, are used interchangeably in this opinion.

[3] The complaint also asserted infringement of plaintiffs' U.S. Patent No. 5,604,213 (the "'213 patent") against Actavis related to Actavis's ANDA No. 208274. (DE 1). The '213 patent expired in December 2016, and on March 21, 2017, the Court entered a stipulation dismissing, without prejudice, plaintiffs' claims of infringement of the '213 patent against Actavis. (DE 318).

[4] On June 19, 2018, Rising Pharmaceuticals, Inc. was substituted for defendant Citron after Citron transferred its ANDA to Rising. (DE 496, 500).

(DE 1).

2. The complaint was dismissed against certain defendants without prejudice, after they all agreed to be bound by any judgment rendered in the 15-5909 action. Those dismissed defendants are Teva Pharmaceuticals Industries Limited; Arab Pharmaceutical Manufacturing Co.; Hikma Pharmaceuticals, PLC; Actavis Pharma, Inc.; Actavis, Inc.; Par; and Citron. (DE 41, 44, 46, 103, 117).

3. On April 20, 2018, plaintiffs and Apotex entered into a license agreement for the '438 patent, and Apotex was dismissed from the action. (DE 467).

4. On September 28, 2015, plaintiffs filed a first amended complaint against Hetero USA Inc., Hetero Labs Limited Unit-V, and Hetero Labs Limited, asserting infringement of the '438 patent related to Hetero's filing of ANDA No. 208349, which sought approval to market generic abiraterone acetate 250 mg tablets. Hetero subsequently withdrew its ANDA, and on March 13, 2017, the Court entered a stipulation dismissing without prejudice plaintiffs' complaint against Hetero. (DE 308).

5. On May 2, 2016, plaintiffs filed a separate action against Amerigen, asserting infringement of the '438 patent related to Amerigen's filing of ANDA No. 208027, which also sought approval to market generic abiraterone acetate 250 mg tablets. (Civ. No. 16-02449, DE 1). This action was consolidated with the 15-5909 action on July 29, 2016 for discovery purposes. (Civ. No. 16-2449, DE 16).

6. On August 25, 2017, plaintiffs filed a separate complaint against Teva and Teva Pharmaceuticals Industries, Ltd., asserting infringement of the '438 patent related to Teva's filing of ANDA No. 210726 for approval to market generic abiraterone acetate 500 mg tablets. (Civ. No. 17-6435, DE 1). Teva Pharmaceuticals Industries, Ltd. was dismissed from this action after it agreed to be bound by any judgment. (Civ. No. 17-6435, DE 10).

7. On January 8, 2018, the 17-6435 action was consolidated with the 15-5909 action for all purposes, including trial, pursuant to Federal Rule of

Civil Procedure 42(a). (Civ. No. 15-5909. DE 381). Teva's ANDA No. 208432 (at issue in the Civ. No. 15-5909 action) is substantively identical to Teva's ANDA No. 210726 (at issue in the Civ. No. 17-6435 action).

B. Metastatic Castration-Resistant Prostate Cancer

8. The invention claimed in the '438 patent treats metastatic castration-resistant prostate cancer ("mCRPC") through a combination of abiraterone and prednisone. (JTX 8000).

9. The prostate is a male genitourinary organ located in the pelvis. (3T530:24-25). Prostate cancer arises when there is an uncontrollable proliferation of prostate tissue. (3T531:2-4). Metastatic prostate cancer occurs when the cancer tumor spreads from the prostate to another organ, such as the bones, liver, or lungs. (3T531:6-8).

10. Male sex hormones, called androgens, promote the growth of prostate cancer cells. (3T531:10, -22 to -24). A first-line treatment for metastatic prostate cancer is androgen deprivation therapy ("ADT"). (1T100:22-25; 3T532:19-20). Starting in the 1940s, the main treatment for prostate cancer was ADT. (1T115:23-116:1). ADT deprives cancer cells of androgens, like testosterone, through either medical or surgical castration. (1T100:24-101:3; 3T532:19-25).

11. ADT is not a cure for prostate cancer; in most patients, ADT eventually loses effectiveness and the cancer may resume growing. (3T533:13-25). At that point the cancer is deemed castration-resistant, as that term is used in mCRPC.

12. Abiraterone, discovered in the early 1990s, is a second-line therapy. (9T1970:24). Abiraterone inhibits the 17α-hydroxylase/$C_{17,20}$-lyase ("CYP17") enzyme. The CYP17 enzyme has a role in the steroid biosynthesis pathway that leads to the production of androgens, including testosterone. (1T123:13-18; 7T1434:4-21; 6T1152:5-9, 1280:1-1281:1; *see* PDX7.5, chart of steroid biosynthesis pathway and abiraterone inhibition, attached as an exhibit to this opinion.)

13. Dr. Johann de Bono, an oncologist and coinventor on the '438 patent, hypothesized that, while abiraterone decreased the production of androgens, it also resulted in an accumulation of "upstream" non-androgenic steroids (*i.e.*, those whose production branches off from the synthesis pathway before the point at which the CYP17 enzyme that is inhibited by abiraterone operates). (1T127:15-16, 128:16-129:3; 3T607:12-14). Those accumulated non-androgenic steroids would activate the androgen receptors on the prostate cancer cells, thereby reducing abiraterone's effectiveness and causing a resistance to abiraterone. (1T128:18-24; 3T607:17-20; *see* top horizontal row of chart, PDX7.5, attached as exhibit.)

14. To combat such resistance, Dr. de Bono hypothesized, a glucocorticoid (the family including prednisone) could be administered to suppress those upstream steroids. (1T127:11-22, 129:8-24).

C. The '438 Patent and Asserted Claims

15. On September 2, 2014, the United States Patent and Trademark Office issued the '438 patent. (JTX 8000). The named inventors of the '438 patent were Alan H. Auerbach and Arie S. Belldegrun. (DE 502, at 86 ¶28). Dr. de Bono was added as an inventor by order of the Court in January 2017.

16. The '438 patent, titled "Methods and Compositions for Treating Cancer," has twenty claims and is directed at methods of treating prostate cancer in humans. (JTX 8000).

17. As described in the '438 patent, it is believed that testosterone and dihydrotestosterone promote the growth of prostate cancer. (*Id.* at 1). The '438 patent further states that hormone therapy can be used to suppress the production or block the effects of hormones like testosterone. (*Id.*). It notes that CYP17 inhibitors have been shown to be useful in the treatment of cancer, and specifically in androgen-dependent disorders like prostate cancer. (*Id.* at 5).

18. The '438 patent discloses such methods as the administration of a CYP17 inhibitor, like abiraterone acetate, in combination with at least one other therapeutic agent, such as an "anti-cancer agent or steroid." (*Id.* at 2).

The '438 patent identifies prednisone as one such therapeutic agent that can be combined with abiraterone acetate. (*Id.*)

19. Claim 1 of the '438 patent, the only independent claim, claims the following:

> 1. A method for the treatment of a prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone.

(*Id.* at 16). Claim 1 is practiced when a "therapeutically effective amount of abiraterone acetate" and a "therapeutically effective amount of prednisone" are administered to a patient with prostate cancer. (3T538:1-11).

20. Dependent claims 2–20 of the '438 patent describe additional limitations of the method, including the amount of abiraterone acetate and the amount of prednisone used, and the type of prostate cancer being treated. Plaintiffs assert infringement of claims 4, 8, 11, 19, and 20 against each defendant.

21. Those dependent claims provide as follows:

a. Claim 4. The method of claim 3, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is about 1000 mg/day.

. . .

b. Claim 8. The method of claim 7, wherein the therapeutically effective amount of the prednisone is about 10 mg/day.

. . .

c. Claim 11. The method of claim 10, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

. . .

d. Claim 19. The method of claim 18, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

. . .

e. Claim 20. The method of claim 17, comprising administering to said human about 1000 mg/day of abiraterone acetate or a

pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

(*Id.*).

D. Claim Construction

22. By Order dated June 27, 2016 (DE 208), the Court adopted the parties' agreed-upon constructions (DE 502, at 89, ¶¶49-51) of the following undisputed '438 patent claim terms:

Claim Term	**Joint Construction**
Preamble: "a method for the treatment of a prostate cancer in a human"	The preamble of claim 1, on which claims 2-20 depend, is limiting and limits the claims to the treatment of a prostate cancer in a human.
"refractory prostate cancer"	"Prostate cancer that is not responding to an anti-cancer treatment or prostate cancer that is not responding sufficiently to an anti-cancer treatment. Refractory prostate cancer can also include recurring or relapsing prostate cancer."
"therapeutically effective amount"	"An amount effective for treating cancer."

23. On November 10, 2016, following a hearing, the Court issued its *Markman*[5] patent claim construction opinion and order. (DE 239, 240, reported at *BTG Int'l Ltd. v. Actavis Labs. Fl, Inc.*, 2016 U.S. Dist. LEXIS 157586 (D.N.J. Nov. 10, 2016)). The parties principally disputed the terms "treatment" and "treating."[6] *Id.* at *5.

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5 *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976-79 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370, 116 S. Ct. 1384, 134 L. Ed. 2d 577 (1996).

6 Defendants sought a broad construction of the term to encompass treatments aimed at not only "reducing the actual prostate cancer, but also 'reducing the pain associated with prostate cancer and replacing the normal production of

24. The Court construed the terms "treatment" and "treating" as "the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer." *Id.* at *54.

E. Clinical Trials and Data

25. There were a number of clinical trials of abiraterone and prednisone. The results of those trials were submitted to the United States Food and Drug Administration ("FDA") to establish the safety and efficacy of abiraterone, with the object of gaining FDA approval to market ZYTIGA®. (2T265:8-12; PDX 2.2 (Summary of Clinical Trials)).

26. Clinical trials proceed in various phases. A Phase I trial is typically the initial drug development, and seeks to determine the safety of administering a particular drug into a human. (2T266:9-12). A Phase II clinical trial uses the findings from Phase I and extends testing to a larger patient population. Those results provide a basis for conducting a Phase III trial, which evaluates clinical efficacy and safety for regulatory approval. (2T266:13-23).

27. In April 2004, Cougar Biotechnology[7] licensed the rights to develop abiraterone from BTG. (1T108:12-13, 230:25-231:4; 8T1817:25-1818:5).

28. In 2004 and 2005, Dr. de Bono designed the first clinical trial of abiraterone, which became known as the COU-AA-001 trial ("001 trial"). (1T108:21-23, 124:17024; PTX 13). The purpose of the 001 trial was to evaluate the safety and efficacy of abiraterone monotherapy in men with mCRPC. (1T126:16-21, 127:23-25).

29. The 001 trial was designed to proceed in two phases. (2T267:3-11). In Phase I of the 001 trial, the dose escalation phase, patients received abiraterone at doses of 250, 500, 750, 1000, or 2000 milligrams. (2T302:7-14).

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glucocorticoids that is blocked when patients are given CYP17 inhibitors.'" *BTG*, 2016 U.S. Dist. LEXIS 157586, at *7.

[7] Cougar Biotechnology is Janssen's predecessor. (2T468:4-5).

In the Phase II portion of the 001 study, all patients received 1000 milligrams of abiraterone acetate. (2T302:20-23).

30. For both phases of the 001 trial, Dr. de Bono proposed an "extension" phase for patients whose cancer had progressed despite the administration of abiraterone. Those patients would receive 0.5 milligrams of a glucocorticoid, dexamethasone.[8] (1T127:11-22, 134:5-14; 2T267:12-18; PTX 11, at 4, 39-40; JTX 8086, at 1).

31. The purpose of this extension study was to evaluate Dr. de Bono's hypothesis that the addition of a glucocorticoid could suppress the upstream steroids, and thus reduce resistance to abiraterone. (1T127:11-22, 128:18-129:3). Dr. de Bono opined that prednisone, another glucocorticoid, would be just as effective as dexamethasone because all glucocorticoids would have a similar effect in terms of suppressing the upstream steroids. (1T132:13-133:20; *see also* 3T618:1-6; 7T1415:5-9). The study was approved by the Institutional Review Board and the Royal Marsden Cancer Research Committee. (1T142:6-8).

32. The 001 study results were published in the Journal of Clinical Oncology. Gerhardt Attard, et al., *Phase I Clinical Trial of a Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms that Castration-Resistant Prostate Cancer Commonly Remain Hormone Driven*, 26 J. of Clinical Oncology 4563 (2008) (JTX 8083) (hereinafter referred to as "Attard 2008"); Gerhardt Attard, et al., *Selective Inhibition of CYP17 with Abiraterone Acetate is Highly Active in the Treatment of Castration-Resistant Prostate Cancer*, 27 J. of Clinical Oncology 3742 (2009) (JTX 8086) (hereinafter referred to as "Attard 2009").

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[8] Dexamethasone and prednisone are both part of the same class of drugs, known as glucocorticoids. (1T133:7-20). Dexamethasone was the steroid used by the institution with which Dr. de Bono was then affiliated, the Institution of Cancer Research ("ICR"), which is at the college of the University of London and the Royal Marsden Hospital. (1T130:1-12, 132:21-24). Dr. de Bono indicated that as to a synthetic steroid, a patients' blood test would reveal the extent to which hormones came from the drug or from a patient's adrenal gland. Prednisone was not then available in the U.K. (1T140:20-25).

33. Even though the central purpose of the Phase I trial was to establish safety, the results of the trial showed that abiraterone alone had anti-tumor activity, measured by a reduction in Prostate-Specific Antigen ("PSA")[9] levels. (1T143:21-23). The 001 trial involved 54 patients. (1T144:1). All received abiraterone. In phase I (abiraterone dose escalation), 15 of the subjects received dexamethasone as well. In phase II (administration of 1000 mg/day of abiraterone), 30 of the subjects received dexamethasone as well. (1T144:1-4). Assuming complete overlap, then, at least 30 patients received combination therapy.

34. When patients developed a resistance to abiraterone monotherapy and a glucocorticoid was added, the anti-cancer effect, measured by PSA declines of at least fifty percent, returned for 10 of the 30 combination-therapy patients in the Phase II portion of the study. (1T144:4-22; 3T588:13-24; JTX 8086). This suggested that a glutocorticoid such as prednisone, at least when administered in combination with abiraterone, has an anti-cancer effect. The suggested mechanism was the suppression of the "upstream" steroids. These upstream steroids, left unchecked, may stimulate prostate cancer growth. (*Id.*; 3T604:20-24, 608:5-18, 663:12-14; 4T861:1-5; *see* top horizontal line of biosynthesis chart, attached.).[10]

35. The second clinical study submitted to the FDA, the COU-AA-002 trial ("002 trial"), was similar to COU-AA-001. (2T268:12-13). The 002 trial, which was conducted in the United States, received FDA approval. (2T269:8-

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9 PSA is one of the modalities used to observe anti-tumor activity for hormone therapy. (1T149:23-25; 2T378:5-18). It is used as a measure of cancer progression. Rising levels of PSA are associated with advancing prostate cancer, while falling levels are associated with control of prostate cancer.

10 Several peer-reviewed articles addressed this finding. *See* Gerhardt Attard et al., *Antitumor Activity with CYP17 Blockade Indicates that Castration-Resistant Prostate Cancer Frequently Remains Hormone Driven*, Cancer Research (2009) (PTX 461, at 4939); Daniel Danila et al., *Phase II Multicenter Study of Abiraterone Plus Prednisone Therapy in Patients with Docetaxel-Treated Castrate-Resistant Prostate Cancer*, 28 J. of Clinical Oncology 1496, 1497 (2010) (JTX 8090); Oliver Sartor et al., *Novel Therapeutic Strategies for Metastatic Prostate Cancer in the Post-Docetaxel Setting*, The Oncologist (2011) (PTX 344, at 1495).

18). Phase I of the 002 trial tested abiraterone monotherapy to determine the best dosage. (2T268:18-19). As originally designed, the Phase II portion of the study was to consist of further abiraterone monotherapy. (2T268:18-19). However, on May 25, 2007, after the results of the 001 study suggested the effect of the glucocorticoid, the protocol of Phase II of the 002 trial was amended. (2T268:19-21, 271:8-12, 272:1).[11] Under that amended Phase II protocol, abiraterone and prednisone would be jointly administered. (2T268:21-23). Patients received 1,000 milligrams of abiraterone and 10 milligrams of prednisone per day. (2T272:4-6). The results of 002 Phase II were published. Charles J. Ryan, et al., *Phase II Study of Abiraterone Acetate in Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer Displaying Bone Flare Discordant with Serologic Response*, Clinical Cancer Research (2011). (JTX 8093).

36. A clinical study report of the 002 trial was submitted to the FDA for its consideration in approving ZYTIGA®. (2T312:16-313:2; DTX 1367). That report included a section that discussed the overall design of the study. (DTX 1367, at 19). In addressing the role of prednisone in Phase II of the 002 trial, the report noted that "all subjects were required to receive low dose glucocorticoids such as prednisone 5 mg twice daily PO or dexamethasone (0.5 mg once daily) with abiraterone acetate to better manage mineralocorticoid side effects." (*Id.*).

37. The conclusion of the 002 study report provided, in full, that:

- In study COU-AA-002, abiraterone acetate demonstrated encouraging antitumor activity as assessed by PSA response by

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[11] The 001 trial, recall, tended to confirm the hypothesis that the disease progression on abiraterone monotherapy was due to an increase in upstream corticosteroids, and that the effect of this increase could be moderated by the addition of a glucocorticoid. (2T273:8-16).

There was some debate at trial as to whether prednisone was added, not in response to the 001 results, but rather in response to a patient's death from a heart attack associated with hypokalemia in March of 2008. (2T274:19; DTX 1354, at 5). The decision to add prednisone in the 002 trial, however, was made in 2007, nearly a year before that patient's death. (2T275:3-4).

PSAWG criteria; objective response by RECIST criteria; and time to PSA progression in this patient population with advanced castration-resistant prostate cancer who had prior hormonal therapies. Importantly, tumor responses to abiraterone acetate were observed in castrate patients who had prior ketoconazole medication.

- Although corticosteroids were not mandated at the initiation of the study, the incidence of mineralocorticoid excess with abiraterone acetate monotherapy was of sufficient frequency to support the routine use of glucocorticosteroids.
- Although the MTD of abiraterone acetate could not be definitely determined based on available data, the doses administered appear to be well tolerated with no DLTs even at 1000mg/day. The results of the study support the use of the 1000 mg daily dose of abiraterone acetate in the treatment of advanced castration-resistant prostate cancer, in view of the antitumor activity and safety observed at this dose.

(DTX 1367, at 110).

38. Dr. Robert Charnas, ZYTIGA®'s global regulatory leader, suggested that because abiraterone and prednisone were tested in combination, their individual anti-cancer effects could not be determined. (2T323:25-324:8).

39. The COU-AA-003 ("003 trial") trial was another study that evaluated 1000 mg/day or abiraterone acetate in post-chemotherapy mCRPC patients. (DTX 1185). The patients in the COU-AA-003 study were allowed to be on steroids. Eighteen of forty-seven patients (38%) were on a low dose of steroids. (DTX 1185.4). PSA declines were seen in thirty-two of the forty-seven patients (68%). The results of this trial were published. Reid, et al., *Significant and Sustained Antitumor Activity in Post-Docetaxel, Castration-Resistant Prostate Cancer with the CYP17 Inhibitor Abiraterone Acetate*, 20 J. of Clinical Oncology 1 (2010). (DTX 1185).

40. The COU-AA-004 Phase II trial ("004 trial") used the combination of abiraterone and prednisone in post-docetaxel mCRPC patients. (2T272:7-19; 3T614:6-15). The median time to PSA progression reported in the COU-AA-003 trial and the COU-AA-004 trial was the same, approximately 5.6 months. (4T954:22-956:11). The results of the 004 trial were also published. Daniel

Danila et al., *Phase II Multicenter Study of Abiraterone Plus Prednisone Therapy in Patients with Docetaxel-Treated Castrate-Resistant Prostate Cancer*, 28 J. of Clinical Oncology 1496, 1497 (2010). (JTX 8090).

41. The COU-AA-301 clinical trial ("301 trial") was the registration study that compared the combination of abiraterone plus prednisone to a control arm of prednisone plus a placebo. (2T276:19-277:3). The 301 trial was considered the pivotal trial showing efficacy and safety for the NDA application. (2T283:5-6).

42. Like previous trials, the coadministration arm of the 301 trial involved 1000 milligrams of abiraterone and 10 milligrams of prednisone, administered daily. (2T277:6-8).

43. Positive effects were seen in the patients receiving abiraterone plus prednisone. The Independent Data Monitoring Committee, an outside committee that evaluates patient safety throughout a clinical trial, therefore recommended that the placebo control arm of the trial be discontinued for ethical reasons. (2T277:12-278:6). All the participants were then given prednisone plus abiraterone, as opposed to a placebo. (2T277:12-17).

44. The 301 trial demonstrated that abiraterone and prednisone in combination were efficacious. (3T372:5-8). The results of the 301 trial demonstrated a four month increase in median overall survival. (2T278:9-13; 2T376:23-25).

45. The results from the 001, 002, 003, 004 and 301 trials were submitted to the FDA for review as part of the original NDA application. (2T284:9-13). No single study compared abiraterone monotherapy to abiraterone plus prednisone combination therapy. (2T293:5-7). Such a comparison by the FDA would necessarily be less direct, based on a comparison of data from different studies. (2T374:12-22).

46. The final clinical trial was the COU-AA-302 clinical trial ("302 trial"). (2T278:16). The 302 trial was the basis for a change to the indications on the ZYTIGA® label in 2018. (2T308:7-8). In the 302 trial, abiraterone plus prednisone was compared to prednisone plus a placebo. The study subjects

were patients whose disease had not progressed to the point where chemotherapy was required. (2T278:18-23). The same dosages, 1000 milligrams of abiraterone and 10 milligrams of prednisone, were administered. (2T279:1-3).

47. In the 302 trial protocol, it was noted that administration of a corticosteroid "improved symptoms of fatigue and tolerability of abiraterone acetate, including symptoms of mineralocorticosteroid excess. The improved tolerability of abiraterone acetate after concomitant administration of low-dose corticosteroids was associated with suppression of ACTH and upstream adrenal steroids[.]" (DTX 1358, at 20).

48. The comparative control arm of this study, as in the 301 study, was discontinued for ethical reasons, to allow all the patients to take abiraterone plus prednisone. (2T279:8-12). The combination of abiraterone and prednisone in the 302 trial showed a sixty percent reduction in the risk of progression or death, and an overall median survival improvement of about four months. (2T279:23-280:2).

F. Prior Art

49. The priority date is August 2006. (DFF at 64, ¶249; PFF at 154, ¶764).

50. Before 2006, there was a significant divergence of opinion within the scientific community as to whether prostate cancer was androgen dependent or independent. (1T116:9-18). However, the prevailing belief was that, once the cancer resumed growing after ADT, the cancer became androgen independent. (1T116:16-18).

51. Prior to the invention described in the '438 patent, there were treatment options for prostate cancer that stopped responding to ADT, but the invention was not among them. (8T1848:18-24; *see* DTX 1135).

52. The relevant prior art consists of the following:

a) Glenn Gerber et al., *Prostate Specific Antigen for Assessing Response to Ketoconazole and Prednisone in Patients with Hormone Refractory Metastatic Prostate Cancer*, 144 J. of Urology 1177 (1990) (DTX 1059) (hereinafter "Gerber 1990");

b) S.E. Barrie et al., *Pharmacology of Novel Steroidal Inhibitors of Cytochrome P450$_{17a}$ (17a-Hydroxylase/C17-20 Lyase)*, 50 J. Steroid Biochem. Molec. Biol. 267 (1994) (DTX 1062) (hereinafter "Barrie 1994");

c) Gerald Potter et al., Novel Steroidal Inhibitors of Human Cytochrome *P450$_{17a}$* (17a-Hydroxylase-C$_{17,20}$-lyase): Potential Agents for the Treatment of Prostatic Cancer, 38 J. Med. Chem. 2463 (1995) (JTX 8037) (hereinafter "Potter 1995");

d) Ian F. Tannock et al., *Chemotherapy with Mitoxantrone Plus Prednisone or Prednisone Alone for Symptomatic Hormone-Resistant Prostate Cancer: A Canadian Randomized Trial with Palliative End Points*, 14 J. Clin. Oncol. 1756 (1996) (DTX 1076) (hereinafter "Tannock 1996");

e) Oliver Sartor, et al., *Effect of Prednisone on Prostate-Specific Antigen in Patients with Hormone-Refractory Prostate Cancer*, 52(2) UROLOGY 252 (1998) (DTX 1087) (hereinafter "Sartor 1998");

f) Michael Jarman et al., *The 16,17-Double Bond Is Needed for Irreversible Inhibition of Human Cytochrome P450$_{17a}$ by Abiraterone (17-(3-Pyridyl)androsta-5,16-dien-3β-ol) and Related Steroidal Inhibitors*, 41 J. Med. Chem. 5375 (1998) (DTX 1085) (hereinafter "Jarman 1998");

g) F.D. Fossa et al., *Flutamide Versus Prednisone in Patients with Prostate Cancer Symptomatically Progressing After Androgen-Ablative Therapy: A Phase III Study of the European Organization for Research and Treatment of Cancer Genitourinary Group*, 19 J. Clin. Oncol. 62 (2001) (JTX 8048) (hereinafter "Fossa 2001");

h) Marwan Fakih et al., *Glucocorticoids and Treatment of Prostate Cancer: A Preclinical and Clinical Review*, 60 Urology 553 (2002) (DTX 1104) (hereinafter "Fakih 2002");

i) Katherine Harris et al., *Low Dose Ketoconazole with Replacement Doses of Hydrocortisone in Patients with Progressive Androgen Independent Prostate Cancer*, 168 J. Urology 542 (2002) (JTX 8053) (hereinafter "Harris 2002");

j) A. O'Donnell et al., *Hormonal Impact of the 17a-Hydroxylase/C$_{17,20}$-lyase Inhibitor Abiraterone Acetate (CB7630) in Patients with Prostate Cancer*, 90 British J. Can. 2317 (2004) (DTX 1129) (hereinafter "O'Donnell 2004");

k) L. Vidal et al., *Reversing Resistance to Targeted Therapy*, 16 J. Chemo. 7 (2004) (DTX 1135) (hereinafter "Vidal 2004");

l) Gerhardt Attard et al., *Selective Blockade of Androgenic Steroid Synthesis By Novel Lyase Inhibitors As A Therapeutic Strategy For*

Treating Metastatic Prostate Cancer, Urological Oncology (2005) (JTX 8072) (hereinafter "Attard 2005");

m) Oliver Sartor, *The Continuing Challenge of Hormone-Refractory Prostate Cancer*, Clinical Genitourinary Cancer (2006) (PTX 108) (hereinafter "Sartor 2006"); and

n) Marc B. Garnick & Camille Motta, *Androgen Deprivation Therapy, the Future*, Prostate Cancer Principles and Practice (2006) (DTX 1157) (hereinafter "Garnick 2006").

53. The prior art is further summarized and discussed at Section II.A.2, *infra*.

G. FDA Approval

54. The FDA will approve a new medication if there is substantial evidence of safety and effectiveness. (2T388:21-22). In order to obtain approval to market a new drug, a company is required to submit a New Drug Application ("NDA") to the FDA. (2T282:4-10, 387:19-388:4). An NDA application contains proposed labeling, prescribing information, animal and human studies, including phase I, II, and III clinical trials, and toxicity data. (2T282:14-283:2, 388:5-12).

55. ZYTIGA® is sold in the United States pursuant to approved NDA No. 202379. (Civ No. 15-5909, DE 502, at 90, ¶53). The NDA application for ZYTIGA® was submitted in December of 2010 for the use of ZYTIGA® in combination with prednisone for the treatment of men with mCRPC. (2T283:19-20, 284:18-21, 370:9-10). The NDA was specifically submitted for ZYTIGA®, and prednisone was considered a concomitant therapy. (2T411:3-5). The application received priority review as requested.[12] (2T284:22-286:13).

56. On November 9, 2010, the FDA and Cougar Biotechnology had a "pre-NDA" meeting. (2T334:3-23, 335:9; DTX 1331). The purpose of a pre-NDA meeting is for the sponsor of a drug and the FDA to discuss the NDA; for the

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[12] The standard timeline for review of an NDA was approximately ten months. Priority review expedites that process, resulting in completion in about six months. (2T285:1-6).

sponsor to inform the FDA about the NDA; and for the FDA to provide initial feedback that would aid in the NDA review process. (2T334:15-23).

57. The scientific rationale for developing abiraterone was addressed in the briefing package that was submitted to the FDA for this pre-NDA meeting. (2T336:5-7; DTX 1331, at 11-14). That scientific rationale was described as follows:

> Based on our understanding of abiraterone acetate's mechanism of action and as predicted by the syndrome of congenital deficiency of CYP17, we anticipated that a state of mineralocorticoid excess mediated by increased deoxycorticosteron could occur after pharmacologic inhibition of CYP17, resulting in hypertension, hypokalemia and fluid retention. Indeed, these mechanism-based toxicities were observed in Phase 1 and 2 studies. Accordingly, the Phase 1 studies were designed to allow administration of low dose corticosteroids for disease progression or for palliation of symptoms. The improved tolerability of abiraterone acetate after concomitant administration of low-dose corticosteroids was associated with suppression of ACTH and upstream adrenal steroids, including mineralocorticoids, suggesting that the combination may be better tolerated and safer regimen in this older prostate cancer patient population.
>
> Thus, the regimen of low-dose prednisone 5 mg twice a day and abiraterone acetate 1 g daily was advanced into Phase 2 and 3 testing. Prednisone was selected over other corticosteroids because it is commonly used as standard of care in combination with chemotherapy and often maintained as palliative treatment after chemotherapy is discontinued in patients with advanced metastatic prostate cancer. When abiraterone acetate was administered in a combination with oral prednisone 5 mg twice daily there appeared to be a decreased incidence and severity of mineralocorticoid based side effects, including hypertension, fluid retention and hypokalemia (Danila et al., JCO). Anti-tumor activity was observed across all patient studies as declines in prostate specific antigen levels, and in objective radiographic responses in the subset of men who had measureable disease.

(DTX 1331, at 12).

58. The NDA as submitted included a "summary of clinical efficacy," *i.e.*, a summary of the clinical trials discussed above that established ZYTIGA®'s efficacy. (2T352:16-353:6; JTX 8187). In comparing the various clinical trials

and addressing efficacy, the report noted that "[t]he totality of data from Phase 1/2 studies, Phase 2 studies, and pivotal Study COU-AA-301 consistently demonstrates the benefit of abiraterone acetate and prednisone treatment for patients with mCRPC." (JTX 8187, at 52; 2T375:8-17).

59. The summary of clinical efficacy explained the specific dosing recommendations of 1000mg/day of abiraterone and 10 mg/day of prednisone. (JTX 8187, at 54). In addressing prednisone, the recommendation provided that "concurrent treatment with prednisone" was "administered to ameliorate mineralocorticoid-related toxicity that was observed with abiraterone acetate in early Phase 1/2 studies." (*Id.*). It noted that when abiraterone was administered alone, "[h]ypertension, hypokalemia, and peripheral edema were observed frequently, and were managed with the mineralocorticoid receptor antagonist eplerenone or with low-dose glucocorticosteroids." (*Id.*).

60. On April 26, 2011, the FDA completed its medical review, which is the FDA's analysis and interpretation of the data presented in the clinical section of the NDA. (2T342:17-343:2; DTX 1333). In addressing the potential for overdose, drug abuse and withdrawal, the medical review included the following comment: "Abiraterone acetate is given concurrently with 10mg of prednisone once daily in order to attenuate mineralocorticoid excess resulting from reduced feedback inhibition of ACTH." (DTX 1333, at 107; 2T344:8-12).

61. The FDA approved the NDA on April 28, 2011. (2T286:19). Specifically, the FDA approved ZYTIGA® in combination with prednisone for the treatment of mCRPC. (2T393:12-17).

62. The FDA publishes Approved Drug Products with Therapeutic Equivalence Evaluations in the "Orange Book." (DE 502, at 97, ¶90). The FDA requires NDA holders to identify in the Orange Book "each patent that claims the drug or a method of using the drug that is the subject of the NDA ... and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product." (*Id.* at ¶91).

63. The '438 patent is listed in the Orange Book in connection with NDA No. 202379. (*Id.* at ¶92). Each defendant had knowledge of the '438 patent and its listing in the Orange Book when each respective defendant filed its Paragraph IV certification for its ANDA. (*Id.* at 98, ¶¶93-94).

H. ZYTIGA Labeling

64. A medication's product label is an FDA-approved document. (2T390:2). The label contains information that the FDA believes is necessary in order for the physician to prescribe a medication properly. (2T390:2-8). The label also reflects the FDA's views about the medication and how it should be used. (2T391:14-17).

65. Physicians look to the Indications and Usage section of a label to determine why a particular therapy is being used. (3T543:8-9). The Warnings and Precautions section of a label provides information about adverse reactions that may occur when using the drug product. (2T420:4-7; PDX 406, at 4). The Dosing and Administration section of a label provides the recommended dose for each indication and subpopulation. (2T412:1-5; 3T543:18-22).

66. On April 28, 2011, the FDA approved NDA 202379, with FDA-approved labeling. (DE 502, at 90, ¶55). The Indications and Usage section provided that, "ZYTIGA is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel." (*Id.* at 90, ¶55).

67. On December 12, 2012, the FDA again approved NDA 202379, with FDA-approved labeling stating in the Indications and Usage section that "ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer." (DE 502, at 90, ¶56).

68. On February 7, 2018, the FDA approved NDA 202379, with FDA-approved labeling stating in the Indications and Usage section that:

> ZYTIGA is indicated in combination with prednisone for the treatment of patients with

- Metastatic castration-*resistant* prostate cancer (CRPC)
- Metastatic high-risk castration-*sensitive* prostate cancer (CSPC)

(PTX 406; emphasis added). This Indications and Usage Section is representative of the Indications and Usage section on the current ZYTIGA® label. (PPF. at 14, ¶68). The Indications and Usage section of the label does not identify any other disease or condition, other than mCRPC and metastatic high-risk CSPC. (4T845:15-17).

69. The approved "Dosage and Administration" section of the 2018 ZYTIGA® label reads, in part:

> **2.1 Recommended Dose for metastatic CRPC**
> The recommended dose of ZYTIGA is 1,000 mg (two 500 mg tablets or four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally **twice** daily.
>
> **2.2 Recommended Dose for metastatic high-risk CSPC**
> The recommended dose of ZYTIGA is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with prednisone 5 mg administered orally **once** daily.

(PTX 406). These are the doses that the FDA has approved for the treatment of these diseases. (2T412:1-2).

70. Section 5 of the ZYTIGA® label, "Warnings and Precautions," warns that it may cause hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess. (PDX 406, at 4). In the 2018 label, the FDA removed the following warning: "[c]o-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in the reduction in the incidence and severity of these adverse reactions." (2T421:13-19).

71. Section 14 of the label highlights some of the clinical studies that were completed and demonstrated efficacy. (2T415:20-22). This section specifies that "[t]he efficacy and safety of ZYTIGA with prednisone was established in three randomized, placebo-controlled, international clinical studies." (PDX 406, at 21; 2T418:1-4).

I. Defendants' Labels

72. Each defendant has filed an ANDA seeking approval to market a generic form of ZYTIGA®, *i.e.*, abiraterone acetate tablets. (DE 502, at 91, ¶65). The FDA requires that a drug manufacturer, when filing for such an application, to prepare a side-by-side comparison of its proposed labels to the brand name labels. (2T398:10-13). Typically, a proposed generic's drug label is substantively the same as the approved branded drug's label. (3T393:10-13).

73. Defendants' proposed ANDA product labels recite the same mCRPC indication as the ZYTIGA® label, except that defendants' labels substitute "abiraterone acetate" for "ZYTIGA." (2T396:18-21, 407:22-24; 3T541:2-24; JTX 8011 (Amerigen's proposed label); PTX 359 (Amneal proposed label); PTX 367 (DRL); PTX 372 (Mylan); PTX 383 (Teva); PTX 393 (West-Ward/Hikman); PTX 397 (Wockhardt)).

74. The proposed Indications and Usage sections of defendants' labels entail that they wish to market abiraterone plus prednisone for the treatment of mCRPC only. (2T408:3-5). The defendants' proposed labels do not contain the mCSPC indication that was added to the ZYTIGA® label in its 2018 version. (2T396:22-397:1).

75. The Dosage and Administration sections of defendants' labels all recommend administering 1000mg/day of abiraterone acetate, and 10mg/day of prednisone. (DE 502, at 94, ¶ 73).

76. Amerigen's, Mylan's, and West-Ward/Hikman's Dosing and Administration sections are identical to the ZYTIGA® pre-2018 labels insofar as they state that the "recommended dosage" is 1,000 milligrams of abiraterone acetate tablets administered orally once daily in combination with 10 milligrams of prednisone administered orally twice daily. (2T413:18-23; JTX 8011; PDX 393).

77. Amneal's, DRL's, Teva's, and Wockhardt's proposed Dosage and Administration sections, like the ZYTIGA® 2018 label, state the same

1000mg/10mg "recommended dosage," while adding the words "for mCRPC." (2T413:23-414:3).

78. The defendants' labels that are based on the ZYTIGA® 2015 label still contain the warning, dropped from the ZYTIGA® 2018 label, that "[c]o-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in the reduction in the incidence and severity of these adverse reactions." (2T422:16-23). The FDA has already instructed Teva to remove this language from its label. (2T424:20-21).

J. ZYTIGA Marketing

79. The FDA requires pharmaceutical companies to submit marketing materials. (2T483:8-10). The materials do not have to be approved in advance, but they cannot mischaracterize a drug's indication. (2T483:23-484:1). Several of ZYTIGA®'s marketing documents discuss the role of prednisone.

80. In a marketing document related to the 2011 indication (*i.e.*, prior to the removal of the warning language related to the "[c]o-administration of a corticosteroid") the role of prednisone was described as reducing "the incidence and severity of mineralocorticoid-related adverse reactions" with ZYTIGA®. (DTX 1260; 2T484:7-23).

81. A ZYTIGA® brochure dedicated to explaining the role of prednisone also notes that prednisone "reduces the incidence and severity of mineralocorticoid-related adverse reactions associated with ZYTIGA." (DTX 1276; 2T488:8-22).

82. A third marketing document explaining the role of prednisone explains that prednisone lessens the system's response to a net cortisol deficit due to abiraterone. (2T489:7-12; DTX 1276).

83. Other ZYTIGA® marketing materials, however, promote ZYTIGA® in combination with prednisone solely as a means to treat prostate cancer. (PDX 424 (stating that "ZYTIGA plus prednisone achieved a statistically significant median overall survival difference"); PDT 447 (stating that "ZYTIGA plus

prednisone significantly increased median radiographic progression for survival")).

II. CONCLUSIONS OF LAW

The Hatch-Waxman Act strikes a balance between two competing policy interests: "(1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market." *Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1370-71 (Fed. Cir. 2002). A brand name drug manufacturer seeking FDA approval must submit an NDA that includes, among other things, a statement of the drug's components, proposed labeling describing the uses for which the drug may be marketed, and scientific data showing that the drug is safe and effective. 21 U.S.C. § 355(b)(1); *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S,* 566 U.S. 399, 404, 132 S. Ct. 1670, 1676 (2012).

The Hatch-Waxman Act streamlines the FDA approval process for generic manufacturers, who can "bring their products to market without submitting all of the extensive drug and clinical data ordinarily required of an NDA under 21 U.S.C. § 355(b)(1)." *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 629 (Fed. Cir. 2015). A generic drug applicant seeking approval to market may file either an ANDA or "505(b)(2) application." 21 U.S.C. §§ 355(b)(2), (j). An ANDA allows generic drug applicants seeking approval "to rely on the safety and efficacy information for an approved drug listed in the Approved Drug Products with Therapeutic Equivalence Evaluations, or the 'Orange Book.'" *Takeda*, 785 F.3d at 629.

After consulting the Orange Book, a generic company filing an ANDA is required to assure "the FDA that its proposed generic drug will not infringe the brand's patents." *Caraco Pharm. Labs.*, 566 U.S. at 406. To achieve this, a generic manufacturer can file a "paragraph IV certification," which states that a listed patent "is invalid or will not be infringed by the manufacture, use, or sale of the [generic] drug." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). The Act treats such a filing as an act of infringement, providing the brand with a right to sue

immediately. *See* 35 U.S.C. § 271(e)(2)(A). Assuming the brand does so, the FDA may not approve the ANDA until thirty months pass, or until the court finds the patent invalid or not infringed. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

Once invalidity is asserted in a paragraph IV certification, the ANDA applicant takes on the burden of establishing it. *In re Cyclobenzeprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1078 (Fed. Cir. 2012). A patent and each of its claims are presumed to be valid, even where those claims may be dependent upon other invalid claims in the patent. 35 U.S.C. § 282(a). A party may rebut this presumption of validity only by clear and convincing evidence. *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) (citing 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 131 S. Ct. 2238, 2245 (2011)).

Once non-infringement is asserted in a paragraph IV certification, the patentee takes on the burden of establishing infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988); *Kegel Co., Inc. v. AMF Bowling, Inc.*, 127 F.3d 1420, 1425 (Fed. Cir. 1997). To prove infringement, the patentee must show that it is more likely than not that the proposed ANDA product would, if commercially marketed, meet the claim limitations of the patent-in-suit. *See Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1287 (Fed. Cir. 2010); *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002).

Plaintiffs allege two kinds of infringement: "induced" and "contributory." *See* 35 U.S.C. § 271(b), (c). Defendants assert the defense of patent invalidity, based on lack of a sufficient written description and obviousness.

I discuss the validity issues first, in section II.A. In subsection II.A.1, I conclude that the '438 patent contains an adequate description. In subsection II.A.2, I hold that the '438 patent is invalid for obviousness. In section II.B, I consider in the alternative whether, if the patent were valid, defendants' activities would infringe. In subsection II.B.1, I hold that the defendants' labels

would result in induced infringement. In subsection II.B.2, I hold that there would be contributory infringement.

A. Validity

As a defense to infringement, defendants assert that the '438 patent is invalid for lack of a written description and for obviousness. Although asserted as a defense, the issue of patent validity is most profitably discussed in advance of the infringement contentions. The defendants prevailed on those invalidity contentions in three inter partes review proceedings ("IPR") before the PTAB. The parties state that the PTAB decisions, dated January 17, 2018, are subject to a pending motion for reconsideration. (DTX 1562 (Mylan decision); *see also* DE 393 (Amerigen and Wockhardt decisions).)[13]

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[13] Defendants do not seek to estop the plaintiffs' litigation of the validity issues that they lost before the PTAB. Rather, the plaintiffs seek to estop defendants from asserting the invalidity of the patent, an issue on which the defendants *prevailed* before the PTAB. That argument was raised *in limine* and previously rejected by this Court. (1T25:24-28:12). Nothing about the trial evidence leads me to reconsider that ruling.

The relevant estoppel provision, 35 U.S.C. § 315(e)(2), concededly may be read in the manner that plaintiffs propose. The manifest statutory intent, however, is to prevent abuse of inter partes proceedings, for example through the withholding of grounds and presentation of serial challenges. As I stated on the record, § 315(e)(2) is "designed to prevent parties from using multiple, possibly inconsistent and wasteful means of attacking a patent . . . . I get it that a party to an IPR has to assert all of its invalidity contentions or risk losing the opportunity to do so."

I do not accept, however, that Congress intended to require a party to stand mute in court because it previously prevailed on the same issue before the PTAB. The result would be a decision reached without consideration of legally relevant facts and issues. And if these Court proceedings overtook review of the PTAB decision, this Court could find itself in the position of being required to enter an injunction against infringement based on a patent already found invalid. *See* 1T25:5–8 ("THE COURT: . . . . Let's just say hypothetically that there was prior art squarely on point. . . . You're saying that having lost in an inter partes proceeding, you could come here and prevail? MR. TRELA: We could prevail until the inter partes proceeding runs its course.")

The case law contains no deep analysis of the issue, but it appears to reflect the concept that only unsuccessful or unsubmitted arguments are subsequently barred. *See Milwaukee Elec. Tool Corp. v. Snap-On Inc.*, 271 F. Supp. 3d 990, 1027 (E.D. Wis. 2017) (Section 315(e)(2) prohibits an *unsuccessful* IPR petitioner from asserting in the district court "that the claim is invalid on any ground that the petitioner raised or reasonably could have raised during that inter partes review.")(emphasis added);

1. Written Description

Defendants allege that the asserted claims in the '438 patent do not meet the written-description requirement of 35 U.S.C. § 112. I disagree.

In pertinent part, 35 U.S.C. § 112 provides:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his [or her] invention.

"The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the [invention] as described in the patent specification." *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2010); *see also AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298 (Fed. Cir. 2014). "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

To begin with, the '438 patent clearly sets forth the metes and bounds of the invention. It teaches the administration of a specified dosage of two specified drugs for the treatment of a specified condition in a specified, narrow class of patients, *i.e.*, those suffering from mCRPC. Not even minimal adjustment or experimentation is suggested; a skilled practitioner (assuming regulatory approval) would need little if any additional instruction to practice the method.

Depomed Inc. v. Purdue Pharma LP, 2014 WL 3729349, at *5 (D.N.J. July 25, 2014) (Bongiovanni, M.J.).

I do not reach the issue of whether in any event the PTAB's decision, which is subject to reconsideration and appeal, is sufficiently "final" for purposes of § 315(e).

In defendants' view, however, the specification is inadequate because it fails to disclose test results showing that prednisone itself provides an anti-cancer benefit. Nor, they say, does it provide sufficient information to permit a POSA to understand that *both* agents, abiraterone and prednisone, "treat" prostate cancer. (DBr. at 68; Def. Response at 38). These challenges fit only awkwardly within a contention that the method is not described so that a practitioner could practice it. Nevertheless, I address them.

First, I find that the specification in the '438 patent sufficiently identifies prednisone as an anti-cancer agent for purposes of the 35 U.S.C. § 122 written-description requirement. As stated in my *Markman* opinion, that is what "treatment," as used here, means. The specification is directed to the administration of abiraterone acetate with "at least one additional therapeutic agent, such as an anti-cancer agent or a steroid." (JTX 8000). The specification defines "anti-cancer agent" as "any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits, stops or reduces the proliferation of cancer cells." (*Id.* at 4). The '438 patent provides a list of anti-cancer agents, including mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, and flutamide. (*Id.* at 3). It further identities additional "anti-cancer" agents as "hormone ablation agents, anti-androgen agents, differentiating agents, . . . antibiotic agents . . . and anti-androgens." (*Id.* at 7). Thus, an antibiotic agent is defined as an anti-cancer agent, and prednisone is explicitly identified as an antibiotic agent. (*Id.* at 9).

Second, the specification provides a list of steroids, including hydrocortisone, prednisone, and dexamethasone. (*Id.* at 3, 10). In discussing the administration of steroids, the specification provides that the "amount of the steroid administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor." (*Id.* at 10). Thus, whether identified as either an "anti-cancer agent" or a "steroid," prednisone is sufficiently identified in the specification as an agent that "treats" cancer.

To this extent, the patent drafter is privileged to act as his or her own lexicographer. "The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Novartis Corp. v. Teva Pharms. USA, Inc.*, 565 F.Supp.2d 595, 604 (D.N.J. 2008) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

Taking the patent's own definitions of terms as my guide, I find that the written description is adequate.

2. Obviousness

Defendants allege that the combination therapy claimed in the '438 patent would already have been obvious to a person of ordinary skill in the art ("POSA") under 35 U.S.C. § 103. The burden here, as in other validity challenges, is proof by clear and convincing evidence. *See* p. 26, *supra,* and cases cited. The parties agree that August 25, 2006 is the priority date for the prior art analysis. Defendants assert that, as of that date, a POSA familiar with the prior art would have been motivated to combine abiraterone acetate with prednisone for three reasons: (1) for its anti-cancer effects; (2) to mitigate abiraterone's side effects; or (3) for prednisone's palliative properties. (DBr. at 33).

A patent claim is invalid as "obvious" where the "differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (citing *In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985) ("Although [the inventor] declared that it cannot be predicted how any candidate will work in a detergent composition, but that it must be tested, this does not overcome [the prior art's] teaching that hydrated zeolites will work.")).

Four factors guide the obviousness inquiry under § 103: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the field of the invention; and (4) objective considerations such as commercial success, long felt need, and the failure of others to develop the invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406, 127 S. Ct. 1727 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684 (1966)). The evidence at trial focused on factors 1, 2, and 4, the prior-art and objective-considerations factors.[14]

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[14] The parties make short work of factor 3, the level of skill possessed by a POSA. Under either side's analysis, that level of skill is quite high. A POSA would be a physician specializing in medical oncology or urology with significant practical experience and with access to individuals with expertise in endocrinology, biochemistry, pharmacology, or other related fields of science.

In determining the level of ordinary skill in the art, the following factors may be considered: "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Envtl. Designs, Inc. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983) (citing *Orthopedic Equip. Co., Inc. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376, 1382 (Fed. Cir. 1983)), *cert. denied*, 464 U.S. 1043, 104 S. Ct. 709, 79 L. Ed. 2d 173 (1984).

Defendants offered the following definition of a POSA:

> Physician specializing in medical oncology or urology, having an M.D. and/or Ph.D. in pharmacology, biochemistry, or related discipline. Significant practical experience (e.g., 5-6 years' worth) in medical oncology or urology could substitute for an advanced degree. It is understood that the POSA would have access to individuals having expertise in pharmacology, biochemistry, endocrinology, enzymology, and/or molecular biology, and would collaborate with them as necessary.

(DTX 2400). Plaintiffs offered the following definition of a POSA:

> A person of ordinary skill would be a physician specializing in urology or medical oncology who has significant practical experience in the treatment of patients with prostate cancer. Such a person would've worked in a team or setting that includes access to one or more individuals who have expertise in endocrinology, biochemistry, pharmacology and/or molecular biology, or related field of science, and who has experience in prostate cancer treatments or androgen synthesis and action.

(3T537:4-12).

Principles specifically governing the application of those factors to a combination patent, especially a combination-therapy patent, are as follows.

The novelty of a combination therapy in relation to prior art may consist in the idea of putting two known elements together. The POSA's motivation to combine prior art teachings to achieve the "claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *Pfizer*, 480 F.3d at 1362 (internal quotation and citation omitted). *Accord Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006) (stating that motivation to modify prior art to arrive at claimed invention "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.") Thus the mix of information available to a POSA must be considered.

Relevance, however, has its limits. There must be "a nexus between the claimed invention and the [objective indicia]." *In re Affinity Labs of Tex., LLC*, 856 F.3d 883, 901 (Fed. Cir. 2017) (quoting *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006)). The evidence, moreover, "must be reasonably commensurate with the scope of the claims." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). To determine whether the necessary nexus exists, "[o]ur cases require consideration of whether 'the marketed product embodies the claimed features.'" *ClassCo, Inc. v. Apple, Inc.*, 838 F.3d 1214, 1222 (Fed. Cir. 2016) (quoting *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000)); *see also Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996) (noting that whether requisite nexus exists is a question of fact).

In reviewing all these factors, courts use an approach that is not formulaic, but "expansive," "flexible," or "functional." *KSR*, 550 U.S. at 415; *see*

The two sides' experts agreed that the discrepancies between their definitions would not affect their opinions.

also Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1291 (2006) ("There is flexibility in our obviousness jurisprudence because a motivation may be found implicitly in the prior art. We do not have a rigid test that requires an actual teaching to combine."). In describing this flexible approach, the Supreme Court noted that, although "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias" in evaluating obviousness, the proper approach must allow for "recourse to common sense." *KSR*, 550 U.S. at 421 (citing *Graham*, 383 U.S. at 36 (warning against "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into use of hindsight")).

The crux of defendants' argument is that the prior art would have motivated a POSA to combine abiraterone with prednisone with a reasonable expectation of success. One component of the defendants' obviousness argument is that the anti-cancer role of prednisone in actual "treatment" of mCRPC could have been anticipated. A second component of the defendants' argument, however, is that the role of prednisone in palliation or reducing side effects would also have motivated a POSA to combine it with abiraterone. Implicit in that second component is the idea that the *motivation* to combine therapies need not have been entirely congruent with the patented *idea* as conceived by the inventor. *See KSR*, 550 U.S. at 420 (stating that it is error to look "only to the problem the patentee was trying to solve"); *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006) ("[T]he skilled artisan need not be motivated to combine [the prior art] for the same reason contemplated by [the inventor]" (quoting *In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992) ("[T]he law does not require that the references be combined for the reasons contemplated by the inventor.")). Thus defendants rely in part on these other effects of prednisone because those effects lent a separate impetus to the administration of abiraterone and prednisone in combination.

The argument can be pushed too far; the proverbial blind pig must at least have been searching for an acorn. The case law does not suggest that

obviousness must be found because an inventor, ignorant of the relevant science and considering an entirely different problem, could have stumbled on the patented method. This case, however, is close to the other end of the spectrum.

The combination therapy, it is true, is patented as a "treatment." But even prednisone's effects as a palliative and a side-effect minimizer would furnish a powerful motivation to combine it with abiraterone. And the idea for such a combination, even if initially motivated only by those two effects, would have gotten the POSA to the same place. That road led straight to the practice of the patented method: the target condition would be prostate cancer; the target population would be the subset of patients who had mCRPC; the dosage would be 1000mg of abiraterone and 10mg of prednisone daily; the object would be to slow the spread of the disease by hormone deprivation; the clinical results would be the same, and would be measured by prolongation of life (or, in the interim, by proxy metrics such as reduction of PSA levels). In short, the anticipated combination therapy—irrespective of what was in the POSA's mind as to the exact mechanism—would have looked precisely the same. So understood, this begins to look less like serendipity and more like inevitability.

I first review the prior art evidence as to abiraterone, prednisone, and combination therapy (subsections a, b, & c). I then review the secondary considerations evidence (subsection d). Finally, I state my overall conclusions as to obviousness (subsection e).

a. *Prior art: abiraterone*

Barrie 1994,[15] a published study involving mice, disclosed that ketoconazole is a non-selective inhibitor that was used as a treatment for hormone-dependent prostate cancer. As a result, efforts were then being undertaken to discover a more potent and selective inhibitor. (DTX 1062, at 1). In that regard, Barrie 1994 concluded that abiraterone was "worthy of further

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15 Full citations and abbreviations for the prior art are at Section I.F, *supra*.

study" as a potential agent "for the treatment of hormone-dependent prostate cancer." (7T1563:7-9; DTX 1062, at 5).

Potter 1995 explained that abiraterone is a "strong candidate for further development as a potential drug for the treatment of prostatic carcinoma in humans." (JTX 8037, at 7; 7T1563:10-13). Abiraterone was also noted as an inhibitor of both the hydroxylase and the lyase function of the CYP17 enzyme. (JTX 8037, at 6; 6T1316:6-16; *see* PDX 7.5, chart attached to opinion). A few years later, Jarman 1998 indicated that abiraterone had been selected for clinical evaluation based on animal testing: "its marked reduction of circulating testosterone levels in the male rat and mouse and of androgen-dependent organ weights in the mouse." (DTX 1085, at 5375).

The first human trial of abiraterone, reported in O'Donnell 2004, began in 1997. (1T109:12-110:1, 209:11-13; DTX 1129). The Institute of Cancer Research tested abiraterone in a Phase I clinical trial. (1T205:24-206:6). No patient was given a glucocorticoid during testing. O'Donnell did, however, discuss co-administration of a glucocorticoid with abiraterone. (1T214:9; DTX 1129; *see infra* at 43).

The O'Donnell 2004 trial comprised of multiple parts. (1T211:3-5). In the first portion of the trial, a population of castrate male patients received a single dose of abiraterone, at varying dosage levels, and were monitored for the following ten days. (1T211:15-20; DTX 1129, at 2319). All patients in this portion of the study experienced a reduction in testosterone levels below castrate levels. (1T214:14-16). The second portion of the trial administered a single dose of abiraterone, at various dosages, in non-castrate males. (1T212:5-7; DTX 1129, at 2319). Testosterone levels were reduced there as well, but not to below-castrate levels. (1T215:4-5). In the third and final portion of the study, non-castrate males were given a single dose of 500 milligrams of abiraterone every day for twelve days. (1T212:8-18, -21). Testosterone suppression was not sustained in that non-castrate portion of the study. (1T214:20-21).

The O'Donnell 2004 trial determined that abiraterone was safe. (1T214:11). But because of the failure to attain sustained testosterone

suppression in non-castrate patients, the results suggested that abiraterone was suitable as a second-line (*i.e.,* post-castration) treatment. (1T216:12-19; DTX 1129, at 2317 ("The enhanced testosterone suppression achieved in castrate men merits further clinical study as a second-line hormonal treatment for prostate cancer.")). Specifically, O'Donnell 2004 found that testosterone levels would be suppressed below castrate levels by a daily dose of abiraterone in the amount of 800 milligrams. (DTX 1129, at 2317; *see also* Garnick 2006 (DTX 1157, at 919-20 (recognizing that abiraterone "shows potential in the treatment of cancer," and "has demonstrated [an] ability to selectively inhibit the target enzyme, resulting in inhibition of testosterone production in both the adrenals and the testes"))). After a series of rejections, the O'Donnell results were eventually published in the British Journal of Cancer, four years after the close of the underlying study. (1T208:2, 222:6-227:17, 239:19-240:1).

O'Donnell 2004 specifically compares ketoconazole to abiraterone. (DTX 1129, at 2318). O'Donnell notes that "[i]n addition to ketoconazole, aminoglutethimide and abiraterone, other compounds designed to inhibit general androgen production have been developed and show promise." (DTX 1129, at 2321). In addressing ketoconazole, O'Donnell 2004 observes that it is an "unselective" inhibitor, that it has an antitumor effect (measured by clinical benefit as well as reduction in PSA), and that a more "selective" (*i.e.,* CYP-17) inhibitor, abiraterone, could be used as a second-line agent. (DTX 1129, at 2318).

b. *Prior art: prednisone*

Tannock 1996 was a palliation study involving patients having refractory prostate cancer with pain. They received mitoxantrone, a chemotherapy drug (not a CYP17 inhibitor) with prednisone, or else prednisone alone. (7T1609:2-12; DTX 1076, at 1756; 8T1742:14-18). Tannock 1996 disclosed that prednisone, dosed at 10 milligrams per day, would provide palliation to hormone-resistant prostate cancer patients, when used with mitoxantrone. (7T1609:1-15; DTX 1076, at 1756). Defendants' expert testified that prednisone

was administered to alleviate the "known effects of mitoxantrone" including nausea, vomiting, hair loss, low blood counts, and neuropathy. (8T1743:2-8).

Sartor 1998 evaluated the effects of prednisone on PSA levels in patients with hormone-refractory prostate cancer. (DTX 1087, at 252). Twenty-nine patients were given ten milligrams of prednisone daily. (*Id.*; 7T1575:5-11). Of those twenty-nine patients, fourteen (48%) achieved a PSA decline of at least 25%, ten (34%) achieved a PSA decline of at least 50%, and four (14%) achieved a PSA decline of at least 75%, measured from baseline. (DTX 1087, at 254). Sartor 1998 reported that four patients (14%) had a duration of response greater than six months. (*Id.* at 254; 7T1575:17-1576:2).

Thus, Sartor 1998 concluded that prednisone could decrease PSA levels. (DTX 1087, at 255; DE 393-3 ("Sartor reasonably stands for the proposition that administration of prednisone is tolerated and effective in a subset of patients, and at the time it was published, indicated some measure of efficacy for certain mCRPC patients."). Sartor 1998 hypothesized that "PSA declines of greater than 50% may be useful in predicting a relatively prolonged survival." (*Id.* at 256).

Fossa 2001 evaluated 201 patients, all of whom had metastatic disease that had progressed after castration. (JTX 8048, at 63). Of those patients, 101 received prednisone and 100 received flutamide, an antiandrogen. (*Id.* at 62). Of the 101 patients treated with twenty milligrams of prednisone per day, twenty-one (20.8%) had a PSA decline of greater than 50%. (7T1578:8-10; JTX 8048, at 63, 67). There was no difference in median overall survival between the two groups of patients, however. (JTX 8048, at 70). Fossa 2001 concluded that "[m]onotherapy with low-cost prednisone should be considered as first-line, standard hormonal manipulation of HRPC, but the combination with tolerable cytotoxic treatment should be explored further." (JTX 8048, at 70).

Fakih 2002, a clinical review article that evaluated "the mechanisms underlying glucocorticoid antitumor effects in prostate cancer," concluded that "[g]lucocorticoids may exert an antitumor effect on androgen-independent prostate cancer by suppression of adrenal androgens. Low-dose glucocorticoids

produce negative feedback on the pituitary gland, leading to a decrease in both testicular and adrenal androgens." (DTX 1104, at 553).

Harris 2002 was a prospective phase II study conducted on twenty-eight men with androgen-independent cancer. It evaluated the efficacy and safety of administering 200 milligrams of ketoconazole, three times a day, with replacement doses of hydrocortisone. (JXT 8053, at 542). Harris 2002 noted that "[g]lucocorticoids alone may have antitumor effects mediated either by direct interaction with androgen receptors or by feedback inhibition of the hypothalamic-pituitary-adrenal axis." (*Id.* at 544).

c. *Prior art: combination therapy*

The study published in Gerber 1990 evaluated PSA level changes in fifteen men with hormone refractory metastatic prostate cancer that were treated with a combination of ketoconazole and prednisone. (DTX 1059, at 1177). The action of ketoconazole is not as focused as that of abiraterone. Abiraterone acetate is a selective drug that inhibits CYP17, one enzyme with two functions: 17 alpha-hydroxylase and 17,20-lyase. (1T123:13-20; JTX 8072, at 3). Ketoconazole is a non-specific inhibitor; it acts on the CYP17 enzyme, but also on other points in the pathways of adrenal steroid synthesis. (1T105:2; 6T1262:10-17, 1326:4-19). Ketoconazole inhibits adrenal steroid synthesis and causes adrenal insufficiency. (6T1276:3-6).

The patients in the Gerber 1990 study were treated with 600 to 900 milligrams of ketoconazole daily and five milligrams of prednisone twice per day. (DTX 1059, at 1177-78). Of the fifteen patients, twelve (80%) had a decrease in PSA levels with a median duration of response of three months. (DTX 1059, at 1177). The other three patients had a prolonged response, greater than eight months, of decreased PSA levels and improvement in bone pain. (DTX 1059, at 1177). Ultimately, Gerber 1990 concluded that "there appears to be a small subgroup of patients with progressive prostate cancer despite androgen ablation who will benefit from ketoconazole and glucocorticoid treatment." (DTX 1059, at 1177).

O'Donnell 2004, discussed in the preceding section, reported promising results for abiraterone. It also indicated, however, that the treated patients experienced a reduced adrenal reserve. (*Id.*; *see also* Attard 2005 (JTX 8072) (noting that all six patients in O'Donnell 2004 "had a reduced cortisol response to ACTH stimulation on the 11th day after dosing, suggesting reduced adrenocortical reserve."). Researchers speculated that such a deficiency could be addressed with a dose of a steroid, either concomitantly or during times of stress. (1T220:24, 221:7-22, 244:12-19, 249:5-9; DTX 1129, at 2317 ("Adrenocortical suppression may necessitate concomitant administration of replacement glucocorticoid.")). In considering the use of a glucocorticoid, O'Donnell 2004 noted that it was "common practice" to administer supplementary hydrocortisone with aminoglutethimide and ketoconazole. (DTX 1129, at 2323).

O'Donnell 2004 suggested that "further studies with abiraterone acetate will be required to ascertain if concomitant therapy with glucocorticoid is required on a continuous basis, at times of physiological stress, if patients become symptomatic or indeed at all." (*Id.*; *see also* Attard 2005 (JTX 8072, at 1245) (concluding that safety and efficacy of abiraterone should be undertaken where abiraterone was administered daily "to castrate men with advanced prostate cancer" and that patients should "be monitored for the development of glucocorticoid insufficiency"); Garnick 2006 (DTX 1157, at 919-20) (noting that abiraterone was under development "as a second-line hormonal therapy for prostate cancer for patients who are refractory;" and that administration of 800 mg/day resulted in "hypersecretion of luteinizing hormone," which "may necessitate concomitant treatment with replacement glucorticoid").

In 2004, Dr. de Bono,[16] along with Lara Vidal, published a review article titled "Reversing Resistance to Targeted Therapy." Its subject matter was

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[16] Defendants now request that the Court disregard parts of Dr. de Bono's testimony, which they say was not properly disclosed before trial. In particular, defendants argue that Dr. de Bono offered surprise expert testimony regarding the import of the prior art and clinical trials. Defendants did not raise this particular

methods of fighting resistance to cancer treatment and thereby maximizing the treatment's anti-tumor effect. (1T113:9-225; DTX 1135). It noted that hormone therapy was the "mainstay" of treating metastatic prostate cancer. (DTX 1135, at 17). Vidal 2004 further observed that circulating low levels of adrenal androgens (*i.e.,* those produced by the adrenal glands rather than the testes) can result in failure to respond to hormone therapy. It further stated, however, that adrenal androgen synthesis can be inhibited by low doses of steroids, or through inhibition of key enzymes using either abiraterone or ketoconazole. (DTX1135, at 7-8).

The authors noted generally that combining drugs could improve outcomes. (1T122:3-4). For example, chemotherapy drugs had been combined to treat lymphoma. (1T122:5-6). Vidal 2004 noted that combination therapies entail "major logistical challenge[s]" since they require "more than one industry partner"; as a result, researchers were pursuing "less selective agents that can hit multiple targets." (DTX 1135, at 11).

Finally, Sartor 2006 noted that "[s]econdary hormonal manipulations (i.e, ketoconazole, estrogens, glucocorticoids, antiandrogens, and antiandrogen withdrawal) have long been used in [hormone refractory prostate cancer], but because no study with these agents has demonstrated a survival advantage, their potential role is not agreed upon by all." (PTX 108, at 238).

d. *Objective considerations*

As to factor 4, objective considerations, plaintiffs raise several arguments related to ZYTIGA®'s commercial success, failure of others, skepticism, long-

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objection during trial, but I nevertheless consider it. (*See* DBr. at 66 (citing 1T98:12-107:7, 113:9-124:16, 130:2-132:12, 136:23-137:7, 142:4-143:15)). The objected-to portions of Dr. de Bono's testimony, while technical, did not exceed the bounds of his personal observations and involvement in the development of the clinical trials. Such testimony is helpful to the court's understanding of the trials and was properly admitted under Rule 701. Fed. R. Evid. 701. *See generally Asplundh Mfg. Div., a Div. of Asplundh Tree Expert Co. v. Benton Harbor Eng'g*, 57 F.3d 1190, 1193 (3d Cir. 1995) (Under Rule 701, even non-experts who possess helpful specialized knowledge may be permitted "to testify about technical matters that might have been thought to lie within the exclusive province of experts.").

felt need, professional approval and industry praise, and unexpected results. My assessment of these is mixed at best, and I give them correspondingly less weight.

As of today, ZYTIGA® has achieved substantial sales and marketplace success. From April 2011 to the end of 2017, plaintiffs estimate, ZYTIGA® generated over $5.7 billion in net sales. (8T1790:17-20). Plaintiffs presented evidence that approximately 85% to 95% of ZYTIGA® prescriptions were being filled in proximity to a fill of prednisone. (8T1803:14-18).

During most of that period of ZYTIGA®'s market success there was a blocking patent in place. Prior to the '438 combination-therapy patent was the patent on abiraterone itself. That patent, U.S. Patent No. 5,604,213 ("the '213 patent"), titled "17-Substituted Steroids Useful in Cancer Treatment," was issued February 18, 1997, and expired in December 2016. (PPF at 208). The '213 patent discusses seventeen steroids and their use in the treatment of androgen-dependent and estrogen-dependent disorders. (JTX 8042). The '213 patent specifically discloses abiraterone and suggests a method of using abiraterone acetate for the treatment of prostate cancer. (*Id.*). The '213 patent compares the inhibition levels of abiraterone with those of ketoconazole, and reports that abiraterone achieves a superior reduction of testosterone levels. (*Id.*). It was under the '213 patent that BTG granted Cougar Biotechnology an exclusive license to develop abiraterone in 2004. (9T2044:21-25).

Plaintiffs point out that two other CYP17 inhibitors had failed to treat advanced prostate cancer (9T1969:24-25); that various pharmaceutical companies declined to pursue abiraterone after 1999 (1T229:10-230:17); and that the O'Donnell 2004 authors had difficulty getting their results published. The anti-cancer effect of abiraterone plus prednisone, then, was unexpected in plaintiffs' opinion. In countering that the argument that ZYTIGA® met a long-felt need, Defendants note that other treatments, in particular Taxotere and Jevtana, had similar survival benefits.

e. *Obviousness: Discussion and analysis*

By the priority date of August 25, 2006, abiraterone had been identified in the art as a treatment for prostate cancer. It was understood that abiraterone selectively inhibited the CYP17 enzyme. This was seen as an improvement on ketoconazole, a less selective agent that inhibited CYP17, but also interfered with other metabolic steps. (*See* O'Donnell 2004; Barrier 1994).

Ketoconazole and aminoglutethimide were known treatments. (6T1260:22-24, 1276:3-6, 1325:13-14, 1327:8-15). Both ketoconazole and abiraterone were steroid inhibitors, and both inhibited the CYP17 enzyme (although, as stated, ketoconazole inhibited others steps as well). (6T1262:7-17, 1325:13-1326:19). Barrie 1994 and O'Donnell 2004 both used ketoconazole as a starting point for their discussions regarding abiraterone and its potential to be a more selective inhibitor.[17] (7T1563:7-9; DTX 1062, at 5; DTX 1129, at 2318). Barrie 1994, comparing the inhibition levels of hormone production by abiraterone with ketoconazole, concludes that abiraterone was more effective than ketoconazole in decreasing testosterone levels. (DTX 1062, at 270; *see also* Jarman 1998 (noting that abiraterone caused "marked reduction of circulating testosterone" warranting further clinical evaluations (DTX 1085, at 5375)). O'Donnell 2004 specifically notes that abiraterone's ability to sustain testosterone suppression in castrate males, when given in 500 to 800 milligram doses, suggested that it could be used as a second-line treatment.[18] (DTX 1129, at 2317).

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[17] The '213 patent likewise used ketoconazole as a starting point and relevant comparison in its discussion of abiraterone. (JTX 8042).

[18] It is undisputed that publication of the study underlying O'Donnell 2004 was delayed, and that companies did not pursue the marketing of abiraterone immediately after that publication. I do not give weight, however, to the plaintiffs' speculation that those events resulted from skepticism about abiraterone therapy, a conclusion unsupported by any first-hand testimony. (PBr. at 34, 39). Because there are many reasons that a company decided not to pursue a particular drug or publish a study, I cannot assume plaintiffs' speculative explanation is the true one.

From all of this, I conclude that abiraterone had been identified in the prior art as a second-line prostate cancer treatment. I also conclude that it was regarded as a superior swap for ketoconazole, in that it performed a parallel function in a more targeted manner.

As for prednisone itself, Tannock 1996 suggested that corticosteroids provide some level of palliation to cancer patients. Sartor 1998 goes farther, and suggests that prednisone can cause reduced PSA levels, a marker of anti-cancer effect. It further teaches the administration of 20 mg/day of prednisone as a monotherapy in patients with mCRPC. Plaintiffs may be correct that Sartor 1998 was flawed, in that it was not a prospective study but a retrospective analysis of data, and that it carried a risk of sample bias. A reference, however, "is prior art for all that it discloses, and there is no requirement that a teaching in the prior art be scientifically tested . . . or even guarantee success . . . before providing a reason to combine." (internal citations omitted); *Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 F. App'x 289, 294 (Fed. Cir. 2011).

Sartor 1998 teaches that prednisone monotherapy worked to reduce PSA levels in some mCRPC patients, and a POSA would have known that. Whether firm or shaky, the Sartor results disclosed to a POSA that prednisone can have an anti-cancer effect. That conclusion is supported by three other prior art references: Fossa 2001, Fakih 2002, and Harris 2002.[19]

Reduced PSA levels, to be sure, do not necessarily correspond to a survival benefit. Still, PSA levels are an accepted measure of progression of prostate cancer. I am not convinced that PSA levels are so meaningless that researchers would have been dissuaded from pursuing prednisone in combination therapy.

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[19] The extent to which the biochemical basis for such an effect was understood is less clear, however, and hindsight is not the appropriate test. *See* Findings of Fact ¶ 34, *supra* (post-priority-date citations).

Based on the foregoing, and some additional references (especially O'Donnell 2004), I find that there was more than sufficient motivation for a POSA to combine abiraterone with prednisone.

Gerber 1990 suggests that a patient whose PSA levels are increasing can be treated with a combination of ketoconazole and a glucocorticoid, which can result in a decrease in PSA levels. Gerber 1990 also teaches that the combination of ketoconazole and five milligrams a day of prednisone, twice daily, is safe and effective for treating hormone-refractory advance prostate cancer.

O'Donnell 2004 corroborates that in the clinical use of ketoconazole, it was "common practice" to administer supplementary hydrocortisone. It states cautiously that "further studies with abiraterone acetate will be required to ascertain if concomitant therapy with glucocorticoid is required on a continuous basis, at times of physiological stress, if patients become symptomatic or indeed at all." (DTX 1129, at 2323). The prior art went so far as to identify specific dosages: between ten and twenty milligrams per day of prednisone (Gerber 1990; Tannock 1996; Sartor 1998; Fossa 2001); and 800 milligrams of abiraterone. (Gerber 1990; O'Donnell 2004; Garnick 2006).

A POSA would have interpreted ketoconazole's clinical use as a basis to take the next investigative steps with abiraterone. It made sense to replace ketoconazole with abiraterone, as it became clear that abiraterone was a superior, more selective inhibitor. Co-administration of 10mg per day of prednisone would naturally carry over from the ketoconazole combination therapy to the abiraterone combination therapy.

I believe a POSA would have been concerned about the potential reduction in cortisol as a side effect of abiraterone's inhibition of CYP17. Specifically, a POSA would have seen the potential for resulting excess mineralocorticoid (aldosterone) and adrenal insufficiency. Plaintiffs'

reservations about the Synacthen test for adrenal insufficiency[20] are, I believe, well-taken. They do not, however, outweigh the clear import of O'Donnell 2004. O'Donnell 2004 states that "[s]ome impact on adrenal reserve was predictable from the steroid synthesis pathway." That conclusion is consistent with defendants' expert's testimony and with the literature relied upon by defendants' expert. (6T1287:3-1292:8; DTX 1096). O'Donnell 2004 suggests that a practitioner could address those side effects through coadministration of a glucocorticoid. To be sure, the paper appears to be agnostic about whether coadministration would (or would always) be necessary. It falls far short, however, of concluding that such coadministration is unnecessary or should be avoided. *See Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (prior art does not teach away "if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed."). I therefore do not agree, as plaintiffs suggest, that prior art "taught away" from the combination therapy. Plaintiffs further suggest that there were other options and theories on how to treat mCRPC, and that there were other anti-cancer agents, perhaps even more promising ones. Nevertheless, the prior art clearly pointed to coadministration of abiraterone with a glucocorticoid. *See, e.g., In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("a finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination."); *In re Gurley*, 27 F.3d 551, 552-53 (Fed. Cir. 1994) (upholding obviousness finding where patent was directed to one of two alternative resins disclosed in prior art reference, even though reference described claimed resin as "inferior.").

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[20] The Synacthen test evaluates adrenal insufficiency based on the measurement of serum cortisol before and after an injection of synthetic ACTH. (DTX 1096).

Nor do I agree that prednisone's own side effects would have discouraged its use. The prior art establishes that, despite side effects, glucocorticoids were reasonably well-tolerated. The mere existence of other treatments does not suggest that a POSA would employ these alternatives to the exclusion of prednisone.

In short, to the POSA, the prior art would suggest that abiraterone could be combined with prednisone with a reasonable probability of success.

The factor 4 objective considerations presented by plaintiffs do not alter my conclusion. *See generally Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991) (holding that district court did not err when it determined that secondary considerations did not carry sufficient weight to override obviousness determination based on primary considerations).

As to the commercial success factor, there can be no dispute that ZYTIGA® has yielded billions of dollars in sales.[21] "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). "Evidence of commercial success . . . is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco*, 463 F.3d at 1311-12. "When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the

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[21] The net sales figures offered by plaintiffs, totaling $5.7 billion for 2011–17, are for ZYTIGA® abiraterone acetate tablets alone. They do not correspond precisely to the patented invention, *i.e.*, ZYTIGA® plus prednisone. *See Merck Sharp & Dohme Corp. v. Sandoz Inc.*, 2015 U.S. Dist. LEXIS 113710, at *118 (D.N.J. Aug. 27, 2015) (Commercial success is measured by sales of a "commercial embodiment of the claimed compound"); *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (noting that "failure to link that commercial success to the features of [the] invention that were not disclosed in [the prior art] undermines the probative force of the evidence."). On that score, plaintiffs offer suggestive though not conclusive evidence that approximately 85% to 95% of ZYTIGA® prescriptions were being filled at a pharmacy in temporal proximity to a fill of prednisone.

patented invention." *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). However, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ormco*, 463 F.3d at 1311-12; *see also J.T. Eaton*, 106 F.3d at 1571 ("[T]he asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art"); *see Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) (noting that if "commercial success is due to an element in the prior art, no nexus exists.").

Specifically, "where 'market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak.'" *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (quoting *Merck*, 395 F.3d at 1377). "A 'blocking patent' is an earlier patent that must be licensed in order to practice a later patent. This often occurs, for instance, between a pioneer patent and an improvement patent." *Prima Tek II, L.L.C. v. A-Roo Co.*, 222 F.3d 1372, 1379 n.2 (Fed. Cir. 2000). "The existence of such a blocking patent may deter non-owners and non-licensees from investing the resources needed to make, develop, and market such a later, 'blocked' invention, because of the risk of infringement liability and associated monetary or injunctive remedies." *Acorda Therapeutics Inc. v. Apotex Inc.*, 2011 U.S. Dist. LEXIS 102875, at *61 (D.N.J. Sep. 6, 2011), *aff'd*, 476 F. App'x 746 (Fed. Cir. 2012); *see also id.* at *66 ("if all other variables are held constant, a blocking patent diminishes possible rewards from a non-owner's or non-licensee's investment activity aimed at an invention whose commercial exploitation would be infringing, therefore reducing incentives for innovations in the blocked space by non-owners and non-licensees of the blocking patent.").

To explain the commercial success of the patented ZYTIGA® combination therapy, despite its alleged obviousness, defendants point to the exclusionary effect of the earlier '213 "blocking patent." Abiraterone was previously known in

the art, and indeed was taught by the '213 patent. From 1997 through 2016, that patent granted its holder the exclusive right to market abiraterone. *See Galderma Labs.*, 737 F.3d at 740 (holding that any inference of non-obviousness gleaned from evidence of commercial success is undermined when blocking patent precludes others from entering market).

Janssen contends that the effect of the blocking patent is overstated, because they were willing to license the '213 patent rights at any time from 2000 until 2004, when Cougar Biotechnology was granted its exclusive license. To be sure, licensing opportunities can "dilute the power of the blocking patent" in evaluating commercial success. *Accord Therapeutics*, 2018 U.S. App. LEXIS 25536, at *70. But such licensing efforts appear to have been lackluster. Dr. Ian Judson testified that he met with three drug companies on one occasion in an effort to partner and license abiraterone. (1T229:23-230:3). Dr. Judson pointed to no further attempts to find a licensing partner. (1T229:12-14). And starting in 2004, of course, both the blocking patent and the Cougar license (which was exclusive) prevented non-owners or licensees from entering the market. Between 2004 and 2006, Cougar Biotechnology was the exclusive licensee for abiraterone. So although the commercial possibilities might otherwise have attracted entrants, Cougar's exclusive status surely would have stifled such interest.

The existence of a blocking patent 1997 through 2006 (indeed, through 2016), despite some desultory licensing efforts, would have discouraged entry at the very time when the obviousness of combination therapy was manifesting itself. *See generally Media Techs. Licensing, LLC v. Upper Deck Co.*, 596 F.3d 1334, 1339 (Fed. Cir.) ("Even if Media Tech could establish the required nexus, a highly successful product alone would not overcome the strong showing of obviousness."), *cert. denied*, 562 U.S. 894, 131 S. Ct. 305 (2010). And the sales of ZYTIGA may not be wholly attributable to the patented combination therapy. These are powerful offsetting factors. All in all, however, I must recognize that this abiraterone product has enjoyed commercial success.

I find the market-skepticism factor to be neutral. "Evidence of industry skepticism weighs in favor of non-obviousness. If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016). Plaintiff advances arguments related to the delayed publication of the study results underlying O'Donnell 2004, a negative comment received in response to those results, the failure to obtain a licensing partner after 1999 and before 2004, the uncertainty of Dr. de Bono's colleagues in proceeding with the extension study, and an article from 1999 that discounted hormonal therapies. Much of that skepticism seems to be directed to abiraterone itself, rather than the claimed combination. And the context is important: as noted above, prior art suggested the combination of abiraterone and glucocorticoids to treat prostate-cancer, and by 1997 industry researchers had patented abiraterone itself. By then, multiple experts had concluded that it was worth pursuing abiraterone as a treatment for prostate cancer. *See* Section II.A.2.a, *supra*. This skepticism factor does not point strongly either way.

I next address the plaintiffs' claims that the patented invention addressed a long-felt need and had unexpected results. "[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem." *Tex. Instruments, Inc. v. U.S. ITC*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). In practical terms, courts "look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need." *P&G v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). "Evidence of 'unexpected results' allows a patent-holder to rebut a *prima facie* case of obviousness by showing that the 'claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.'" *Daiichi Sankyo Co., Ltd. v. Mylan Pharm. Inc.*, 670 F. Supp. 2d 359, 382 (D.N.J. 2009) (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995), *aff'd*, 619 F.3d 1346 (Fed. Cir. 2010)). To establish this

factor, "the claimed properties or results must be different in 'kind and not merely in degree' from the results of the prior art." *Id.* (quoting *In re Huang,* 100 F.3d 135, 139 (Fed. Cir. 1996)). That is, in order for the results to be "unexpected," they must be proven to be surprising in relation to the closest prior art. *Id.* (citing *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)).

Plaintiffs state that the claimed invention was an advance on the prior art in that it had less toxicity, was better tolerated, and improved overall survival. Defendants point to existing contemporaneous alternatives: Jevtana was approved by the FDA in 2010, a year before ZYTIGA® was approved; Xtandi was approved in 2012. (7T1626:13-18). Those drugs were FDA-approved and available for the treatment of prostate cancer patients. *Cf. Pfizer Inc. v. Teva Pharm. United States, Inc.*, 460 F. Supp. 2d 659, 662 (D.N.J. 2006) (noting that failure to obtain FDA approval is "appropriate benchmark in evaluating failure of others"). Taxotere (a chemotherapy drug) and Jevtana were found to extend overall survival of mCRPC patients by 2.5 months, whereas ZYTIGA®-based therapy extended survival by about four months. (7T1622:17-24). That represents a real improvement, but an incremental one. In the context of prostate cancer patients with dire prognoses, it cannot be discounted. Still, it does not suggest that all other efforts had failed, or that the abiraterone/prednisone combination therapy was unexpected "in kind and not merely in degree." *Daichi, supra.* So, although there is evidence supporting the unmet-need or failure-of-others factors, I do not find it to be powerful.

As for the professional-approval factor, plaintiff points to the 301 and 302 studies, as well as the post-priority-date Attard 2008 and 2009 references. "Appreciation by contemporaries skilled in the field of the invention is a useful indicator of whether the invention would have been obvious to such persons at the time it was made." *Vulcan Eng'g Co. v. FATA Aluminium, Inc.*, 278 F.3d 1366, 1373 (Fed. Cir.), *cert. denied,* 537 U.S. 814, 123 S. Ct. 81 (2002). A court may look to "contemporaneous recognition of the achievements of the

[patented] system, including articles in trade journals" and testimony by those skilled in the art that prior to the appearance of the patented technology, it was generally believed the system could not be created. *Id.* This factor weighs somewhat in plaintiffs' favor.

All in all, however, I conclude that the patented combination here was well foreshadowed in peer-reviewed articles. That factor outweighs the others. Balancing all of the prior art and the other indicia, I find that the evidence favors a conclusion of obviousness. *Tokai Corp. v. Easton Enters.*, 632 F.3d 1358, 1370 (Fed. Cir. 2011) ("However, even assuming the existence of a nexus, we see no error in the district court's determination that Tokai failed to establish 'that any of these secondary factors are significant,' . . . in light of the strong showing of prima facie obviousness.").

Defendants' burden of proof to rebut the presumption of validity by clear and convincing evidence is met. The '438 patent is declared invalid for obviousness.

B. Infringement

In this section, I assume *arguendo* that the '438 patent is valid and consider whether, if valid, it would have been infringed. Plaintiffs assert both induced and contributory infringement. Both, I find, would be supported by a preponderance of the evidence.

1. Induced infringement

The gist of the induced infringement claim here is that the ANDA label, which specifies indications and proper use of the abiraterone/prednisone combination therapy, would induce physicians' direct infringement of the method claimed in the '438 patent. The label by definition embodies the range of uses and indications that are approved by the FDA. Defendants argue that because the allegedly infringing use would fall outside the scope of the FDA-approved use, the ANDA label does not induce infringement.

It's a subtle argument. Both the patent and the label indications, followed faithfully, would lead to the same actions, undertaken in the same manner and for the same reason: the administration of abiraterone and

prednisone, in combination, to treat a class of patients who suffer from mCRPC, with the goal of slowing the progression of the disease. The defendants, however, argue that the '438 patent claims that *each* component (abiraterone, prednisone) has an anti-cancer effect. The FDA, in contrast, allegedly approved administration of the prednisone component of the combination only for its palliative effect, or to address side effects. Therefore, the argument runs, the administration of the combination therapy in accordance with the FDA-approved label would not infringe.

Defendants ask, in effect, that the court look behind the Indications and Usage section of the label, which provides for combination therapy and does not segregate the contribution of each component. That would require the Court to reanalyze the clinical data as if it were a regulatory body, and posit a revised Indication which, in defendants' estimation, would better fit the underlying science. I do not sit to reconstruct a theoretical ruling by an ideal FDA; in assessing the scope of the FDA approval, I am confined to the actual ruling of the actual FDA. In short, this is not an appeal of the FDA's decision, but only an attempt to define its scope.

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b); *see Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). Thus infringement liability falls upon parties who, while not directly infringing a patent themselves, induce others to infringe. *See Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1926 (2015).

"A person induces infringement under § 271(b) by actively and knowingly aiding and abetting another's direct infringement." *C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 675 (Fed. Cir. 1990) (emphasis omitted). To succeed on an induced infringement claim, a plaintiff must prove that the defendants' "actions induced infringing acts and that [they] knew or should have known [their] actions would induce actual infringement." *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990). However, it is insufficient that defendants merely have "knowledge of the acts

alleged to constitute infringement." *Id.* "[P]roof of actual intent to cause the acts which constitute the infringement is a necessary prerequisite to finding active inducement." *Hewlett–Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990); *see ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007). "While proof of intent is necessary, direct evidence is not required; rather, circumstantial evidence may suffice." *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668 (Fed. Cir. 1988).

a. FDA approval

The '438 patented method, say defendants, requires that *each* component (abiraterone and prednisone) have an anti-cancer effect. The FDA however, allegedly approved the prednisone component for its palliative effects only, and the proposed ANDA labels reflect that. Thus, according to defendants, their ANDAs do not meet the claim limitation of a "therapeutically effective amount of prednisone," *i.e.*, an amount of prednisone that is, in itself, therapeutically effective *against prostate cancer.*

How do we know that the FDA did not approve a therapy in which prednisone, viewed separately, has an anti-cancer effect? Primarily, defendants say, because (1) the underlying clinical trials and data provided to the FDA would not permit such a conclusion. Relatedly, defendants cite the following evidence: (2) the ZYTIGA® label is vague in its Indications and Usage section as to the role of prednisone; (3) plaintiffs' NDA submissions focused on the efficacy of abiraterone, not prednisone, in treating cancer; (4) the FDA approval package does not suggest that prednisone was approved for its combination effect with abiraterone; and (5) the FDA-approved marketing materials promote prednisone as relieving abiraterone's side effects.

"The FDA-approved label for an approved drug indicates whether the FDA has approved a particular method of use for that drug." *Bayer Schering Pharma AG & Bayer HealthCare Pharm., Inc. v. Lupin, Ltd.*, 676 F.3d 1316, 1322 (Fed. Cir. 2012). Under the Food, Drug, and Cosmetics Act ("FDCA"), new pharmaceutical drugs cannot be marketed or sold unless the sponsor of the

drug demonstrates to the satisfaction of the FDA that the drug is "safe for use under the conditions prescribed, recommended or suggested" on the drug's label. 21 U.S.C. § 355(d). A drug receives FDA approval only for treatment of specified conditions, referred to as "indications." 21 U.S.C. §§ 352, 355(d).

FDA regulations provide guidance on how to interpret a label. The "Indications and Usage" section of the label must set forth indications that are supported by "substantial evidence of effectiveness based on adequate and well-controlled studies." 21 C.F.R. § 201.57(c)(2)(iv). The Indications and Usage section "must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition." 21 C.F.R. § 201.57(c)(2). "Indications or uses must not be implied or suggested in other sections of the labeling," *i.e.*, sections other than the Indications and Usage section. 21 C.F.R. § 201.57(c)(2)(iv); *cf. Warner-Lambert*, 316 F.3d at 1356 ("The FDA does not grant across-the-board approval to market a drug. Rather, it grants approval to make, use, and sell a drug *for a specific purpose* for which that drug has been demonstrated to be safe and efficacious." (emphasis added)).

The three cases cited by the defendants, *Bayer Schering, supra, Warner-Lambert, supra,* and *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1324-25 (Fed. Cir. 2003), are not precisely on point. To begin with, they involve multiple effects of a single drug, rather than a dispute over the allocation of multiple effects as between two drugs. I take my lead, however, from those cases' shared reluctance to adopt the mode of analysis of the FDA approval that is employed by the defendants here.

Because *Bayer Schering* is the most pertinent of the three, I give it the most extended discussion. There, the defendants sought to market a generic form of Yasmin, a branded oral contraceptive. The FDA had granted plaintiffs' NDA seeking approval of Yasmin "for oral contraception." 676 F.3d at 1319. The defendants' ANDAs sought FDA approval to market generic forms of

Yasmin for the same approved use, "oral contraception." *Id.* Defendants filed paragraph IV certifications, and the plaintiffs filed suit against the ANDA applicants, alleging infringement of a method-of-use patent. That patent's claims recited that the drug "achieves three effects simultaneously: a contraceptive (or gestagenic) effect, an anti-androgenic effect . . . and an anti-aldosterone effect." *Id.* at 1320. Defendants filed a motion for judgment in their favor on the pleadings; they would not infringe, they said, because they sought to market the generic form of Yasmin "only for oral contraception and not for the combination of uses claimed in the [] patent." *Id.* The district court agreed. *Id.*

On appeal, the plaintiffs acknowledged that both the FDA-approved label and the proposed generic labels stated in their Indications and Usage sections that the drug was to be used as an "oral contraceptive." *Id.* at 1320. The "Clinical Pharmacology" section of the label, however, referred to the other two effects, *i.e.*, the anti-androgenic and anti-aldosterone effects. Based on that language, the plaintiffs argued that the FDA had approved "the use of Yasmin to induce those effects" in addition to the contraceptive effect. *Id.* at 1322, 1324.

The Federal Circuit held that, as to this issue, it is the Usages and Indications section that does the real work. The court expressly rejected the notion that an indication could be implied from another section of the label, an approach that would not make regulatory sense. A particular use or indication for a drug is FDA-approved only when the safety and efficacy of that use has been established. The inclusion of such a use in the label's Indications and Usage section constitutes the necessary "[a]cknowledgement of the safety and efficacy of that specific method of use." *Id.* at 1324.

Mention in the Clinical Pharmacology section, the court held, is not the same thing at all:

> The reference in the Clinical Pharmacology section of the label to the anti-mineralocorticoid and anti-androgenic activity of drospirenone is certainly not a direct indication of an appropriate

> use for Yasmin, and even if it could be considered an "implied or suggested" indication of an appropriate use, the regulation expressly states that such implied or suggested uses do not constitute approved uses.

Id. at 1323.

The Federal Circuit in *Bayer Schering* discussed extrinsic evidence submitted by the plaintiffs, including physicians' declarations and marketing materials. *Id.* at 1324. These documents, said the plaintiffs, established a context that suggested FDA approval of Yasmin as safe and effective not just for contraception, but for the claimed combination of three effects. *Id.* The Federal Circuit demurred. This evidence, the Court held, demonstrated that the FDA was *aware* that Yasmin could cause the other two effects, not that the FDA had *approved* the safety and efficacy of the medication for the claimed combination of effects. *Id.* Accordingly, the Court held that the FDA had approved Yasmin for use only as an oral contraceptive, and that defendants did not commit infringement. The defendants sought to market their drug solely for that approved use as a contraceptive, while the patent claimed the trio of uses in combination. *Id.* at 1326.

Following the lead of *Bayer,* I will not read an indication into the ZYTIGA® label or ANDA labels that is not there. The Indications and Usage section is clear that abiraterone and prednisone are to be used in combination for the treatment of mCRPC. That indication signifies that these agents are FDA-approved in combination to treat cancer. (2T400:16-24).

Defendants' FDA expert, Dr. Akhilesh Nagaich, testified persuasively that prednisone would not have been identified in the Indications and Usage section if its sole approved purpose were the treatment of side effects, and I agree. (4T861:21-862:2). I also credit Dr. O'Shea's testimony, which is consistent with the FDA regulations, that if prednisone were approved solely to treat side effects of abiraterone, it would probably not appear in the Indications section, but only in the label's dosage and administration section, or the warnings and precautions section. (2T401:19-402:1, 405:1-6). It is also likely that if

prednisone had been approved only to alleviate side effects, the label would simply have said so. (2T402:2-3).

An item's inclusion in the Indications and Usage section cannot be brushed aside; to place it there is a critical regulatory decision. Indeed, as noted above, it's essentially that or nothing; indications *not* listed in the Indications and Usage section cannot be derived by implication from other sections of the labeling. 21 C.F.R. § 201.57(c)(2)(iv) ("Indications or uses must not be implied or suggested in other sections of the labeling"); *see also Bayer Schering*, 676 F.3d at 1323–24; *Warner-Lambert*, 316 F.3d at 13; *Shire LLC v. Amneal Pharm., LLC*, 2014 U.S. Dist. LEXIS 85369, at *18 (D.N.J. June 23, 2014) (rejecting argument that drug was FDA-approved to treat amphetamine abuse based on studies section of label, where the Indications section clearly stated that the drug was "indicated for the treatment of Attention Deficit Hyperactivity Disorder"), *aff'd and reversed on other grounds*, 802 F.3d 1301 (Fed. Cir. 2015).[22]

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[22] I consider with care certain other cases in which courts were considering, *inter alia,* the related but distinct issue of specific *intent* to induce infringement. *See* Section II.C, *infra.* With that caveat, I have given some weight to cases that that have rejected invitations to infer a drug's use from sections of the label other than indications and usage.

Thus, in *United Therapeutics Corp. v. Sandoz, Inc.*, No. 12cv1617, 2014 U.S. Dist. LEXIS 121573, at *49 (D.N.J. Aug. 29, 2014) Judge Sheridan of this court persuasively rejected a plaintiff's argument that an infringing use could be predicated on a label warning, as opposed to an indication. The court noted that there is a "rather significant difference between a warning and an instruction." *Id.* A "warning provides information regarding a potential risk," but stops short of prescribing a specific "course of action." *Id.* An instruction, on the other hand, specifically directs that a particular action, or series of actions be taken. *Id.* at 49-50 (rejecting inducement claim if patentee must engage in "scholarly scavenger hunt" through the label to identify statements that may potentially, but not inevitably, impact a prescribing physician's actions).

To similar effect is *Otsuka Pharm. Co., Ltd. v. Torrent Pharm. Ltd., Inc.*, 99 F. Supp. 3d 461, 476, 490-93 (D.N.J. 2015) (Simandle, C.J.) (finding that warning and safety information is insufficient to establish inducement of claimed method). *See also Sanofi v. Glenmark Pharm. Inc.*, 204 F. Supp. 3d 665, 674 (D. Del. 2016) (finding that physician would look to indications and usage section, but that the indications and usage section explicitly referred physicians to the clinical studies section, which a physician would therefore consider as well), *aff'd*, 875 F.3d 636 (Fed. Cir. 2017).

Also implicit in *Bayer* is my refusal to give controlling weight to the other evidence introduced by defendants. To be sure, there are indications in the record that the FDA was aware of prednisone's palliative benefits. To be sure, underlying NDA submissions emphasize the anti-cancer effect of abiraterone rather than that of prednisone. And there there are marketing materials that tout the palliative effects of prednisone without mentioning its anti-cancer effect. Giving these proofs due latitude, I nevertheless conclude that they do not negate what the FDA actually did in its approval of the label's Indications and Uses. *See Bayer Schering,* 676 F.3d at 1323-24 (refusing to imply indication from marketing materials, clinical pharmacology section of label at issue, and from physician's declarations). I cannot find that prednisone was approved as part of ZYTIGA®'s indication solely for its benefits with respect to palliation and side effects.

Concededly, this Court, like the parties, must wrestle with an irreducible level of ambiguity in a combination-therapy approval. As defendants say, the Indications and Uses do not, for example, attribute a percentage of efficacy to each component; the most that can be said is that the FDA has approved the combination as safe and effective. Similarly, defendants attack plaintiffs' cited combination-study clinical trials which, in defendants' view, are confounded and fail to establish the independent contribution of prednisone to the efficacy of the combination.

Again, the fact remains that the FDA did approve the combination-based treatment of mCRPC based on a combination study. Perhaps the studies could have been better designed. Perhaps the researchers could have found an ethical means of definitively isolating the contribution of each component.[23]

For similar reasons, I do not give weight to the warning that was omitted from the 2018 version of the ZYTIGA® label ("Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in the reduction in the incidence and severity of these adverse reactions." (2T421:13-19)).

[23] Placebo control studies, for example, were discontinued when the combination therapy began to show therapeutic benefit. *See* Section I.E., *supra.*

But from arguments that the FDA *should* not have approved an indication, I cannot leap to the conclusion that it *did* not. That, to me, is an important methodological lesson to be drawn from the approach of *Bayer*.

I treat defendants' other two cited cases more briefly. In *Warner-Lambert*, the branded manufacturer held a patent for a method of "treating neurodegenerative diseases" using a drug known as gabapentin. 316 F.3d at 1351. Its NDA, however, led to approval of gabapentin for use in "adjunctive therapy in the treatment of partial seizure with and without secondary generalization in adults with epilepsy." *Id.* at 1352. Defendant Apotex's ANDA sought to market generic gabapentin for the same indication, *i.e.*, partial seizure. *Id.* The Federal Court affirmed the grant of summary judgment to Apotex because the two indications were distinct; partial seizure is not a neurodegenerative disease. *Id.* at 1353.

Finally, in *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1324-25 (Fed. Cir. 2003), the Federal Circuit held that an ANDA applicant's labeled indication for reducing intraocular pressure would not induce infringement of patented methods of "protecting the optic nerve and retina" and "providing neural protection." Because the patent-claimed uses were not approved by the FDA, the ANDA applicant could not be held liable for infringement even if the proposed drug in fact had those additional protective effects in patients who took the drug for the approved purpose. *Id.* at 1324.

These three cited cases, *Bayer* in particular, eschewed the kind of searching review of the FDA record and regulatory "do-over" that defendants propose. The common feature of these three cases is that, to decide the induced-infringement issue, those courts compared the wording of the label to the patent claims.[24]

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[24] What may be occurring here is a kind of category mistake. This is not an appeal seeking affirmance or reversal of an FDA decision. In this context, what is significant about an FDA approval is its existence and scope.

Following that approach, I find that the combination therapy embodied in the label meets the claim limitations of the patent. The Indication on the ZYTIGA® label is clear: "ZYTIGA is indicated in combination with prednisone for the treatment of patients with Metastatic castration-resistant prostate cancer (CRPC)." (PTX 406). That language aligns with the language of Claim 1 of the patent: "A method for the treatment of a prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate . . . and a therapeutically effective amount of prednisone." (JTX 8000).

Although the Indications and Usage section is paramount, I observe that the dosing section and the clinical studies section corroborate the reasoning above. The 301 study established that the combination of the two drugs has an anti-cancer effect. Section 14 of the label, which highlights the clinical studies that were completed, states that "[t]he efficacy and safety of *ZYTIGA with prednisone* was established in three randomized, placebo-controlled, international clinical studies." (PDX 406 at 21 (emphasis added); 2T418:1-4). The effectiveness seen in the studies is attributed to abiraterone plus prednisone, not simply abiraterone. (2T418:6-7; 3T588:5-7). The dosing section recommends that both drugs be administered in specific doses for the purpose of treating mCRPC. In short, it is the combination, and not one drug to the exclusion of the other, that was found safe and effective as a treatment for mCRPC. The FDA meant what it said when it listed the combination in the approved Indications and Uses.

The ZYTIGA® Indications and Usage section encompasses an FDA-approved method, the administration of abiraterone plus prednisone for the treatment of mCRPC. That being the patented method, I find that the labels encompass infringement.

b. Intent to induce infringement

The next, interrelated question is whether the ANDA defendants' proposed abiraterone labels evince a specific intent to encourage physicians to

infringe the '438 patent. To summarize, the '438 patent claims the administration of a "therapeutically effective amount of abiraterone acetate" and a "therapeutically effective amount of prednisone," which is defined in dependent claims as 1000mg/day of abiraterone and 10 mg/day of prednisone, to a mCRPC patient. I find that the labels embody an intent to induce a physician to do just that.

Inducement can be established "where there is '[e]vidence of active steps taken to encourage direct infringement,' which can in turn be found in 'advertising an infringing use or instructing how to engage in an infringing use.'" *Takeda*, 785 F.3d at 630–31 (quoting *Metro–Goldwyn–Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936, 125 S. Ct. 2764, 162 L.Ed.2d 781 (2005)). "[T]he sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent, and usually is also contributory infringement." *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011) (citing *Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (finding intent to induce infringement based on product label authorizing patented use, which "would inevitably lead some consumers to practice the claimed method"); *DSU Med. Corp. v. JMS Co. Ltd.*, 471 F.3d 1293, 1305-06 (Fed. Cir. 2006) (*en banc* in relevant part) (finding liability for induced infringement when company "offers a product with the object of promoting its use to infringe, as shown by clear expression or other affirmative steps taken to foster infringement")). If relying on instructions, those instructions must evince an "intent to encourage infringement." *Vita–Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 (Fed. Cir. 2009). It is not enough that the instructions happen to encompass an infringing mode; rather, they must "teach an infringing use . . . such that we are willing to infer from those instructions an affirmative intent to infringe the patent." *Vita-Mix*, 581 F.3d at 1329 n.2; *see Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1365 (Fed. Cir. 2012). When proof of intent to encourage depends on the label, "[t]he label must encourage, recommend, or promote infringement." *Takeda*, 785 F.3d at 631 (citations omitted).

Mind-reading, however, is not required to establish the necessary intent. The sale of a product specifically labeled for use *via* a patented method constitutes inducement to infringe that patent. *Astrazeneca*, 633 F.3d at 1060 (finding intent to induce infringement based on the product label authorizing patented use, which "would inevitably lead some consumers to practice the claimed method.").

With this framework in mind, the Court analyzes whether the ANDA labels bespeak an intent to induce infringement by doctors. Defendants' proposed product labels, recall, are substantively identical to the approved ZYTIGA® label, except that the chemical name "abiraterone acetate" is substituted for the trademark "ZYTIGA®."

Defendants' Indications are as follows:

- Amerigen's Indication provides "Abiraterone acetate tablets are a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer[.]" (JTX 8011);
- Amneal's Indication provides "Abiraterone acetate tablets are a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with . . . metastatic castration-resistant prostate cancer (CRPC)." (PTX 359);
- DRL's Indication provides "Abiraterone acetate is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with . . . metastatic castration-resistant prostate cancer (CRPC)." (PTX 367);
- Mylan's Indication provides "Abiraterone acetate tablets are a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with . . . metastatic castration-resistant prostate cancer (CRPC)." (PTX 372);
- Teva's Indication provides "Abiraterone acetate tablets are a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with . . . metastatic castration-resistant prostate cancer (CRPC)." (PTX 383);
- West-Ward/Hikman's Indication provides "Abiraterone acetate tablets, USP are a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with . . . metastatic castration-resistant prostate cancer (CRPC)." (PTX 393); and

- Wockhardt's Indication provides "Abiraterone acetate tablets, USP are a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with . . . metastatic castration-resistant prostate cancer (CRPC)." (PTX 397).

The Indications and Usage section of defendants' labels, no less than that of the ZYTIGA® label itself, clearly express an intent that physicians be authorized to prescribe abiraterone plus prednisone for the treatment of mCRPC. (2T408:3-5).

Again, the Indications and Usage section is paramount, but I find corroboration elsewhere. The approved "Dosage and Administration" section of the 2018 ZYTIGA® label reads, in part: "Recommended Dose for metastatic CRPC . . . The recommended dose of ZYTIGA is 1,000 mg (two 500 mg tablets or four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily." (PTX 406).

Defendants' labels all contain Dosage sections that recommend administering 1000mg/day of abiraterone acetate, and 10mg/day of prednisone. (DE 502, at 94 ¶73). Amneal's, DRL's, Teva's, and Wockhardt's proposed Dosage sections track the wording of ZYTIGA®'s 2018 label. (2T413:23-3). They state the recommended "recommended dosage *for mCRPC*." (2T413:25-414:3 (emphasis added)) The other defendants' labels track the pre-2018 ZYTIGA® label in that they state the "recommended dosage" but omit the words "for mCRPC." I do not regard the distinction as significant; everyone agrees that the relevant target group for the ANDA consists of mCRPC patients.[25]

The similarities between plaintiffs' and defendants' Indications and Dosing sections are manifest. Defendants nonetheless contend that this, in

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[25] The 2018 ZYTIGA® label, recall, added an indication for mCSPC (*i.e.*, the castration-sensitive, as opposed to castration-resistant, form of the disease). Presumably the "for mCRPC" language was felt to be necessary for clarity, since the label now had more than one indication. I do not believe it alters the substance of the label. At any rate, the ANDA parties do not seek to market the drug combination for that additional mCSPC indication.

itself, is not sufficient to establish inducement because the labels do not direct doctors to use prednisone to fight cancer, as opposed to addressing abiraterone's side effects. (DBr. at 27). In a similar vein, defendants argue that they do not "know" that prednisone has anti-cancer effects. Lacking such knowledge, defendants say, they cannot be regarded as intentionally promoting such use. (DBr. at 29).

The intent required here is not the kind of specific intent required by the criminal law. In the context of patent infringement litigation involving pharmaceuticals, "the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent." *Eli Lilly*, 435 F. App'x at 926; *see also Astrazeneca*, 633 F.3d at 1060 (product label authorizing patented use sufficient to establish intent, because it "would inevitably lead some consumers to practice the claimed method"); *GlaxoSmithKline LLC v. Glenmark Generics Inc., USA*, 2015 U.S. Dist. LEXIS 52525, at *18 (D. Del. Apr. 22, 2015) ("there is no question that statements 'in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement' for purposes of an induced infringement claim." (citation omitted)).

The key question is whether the label teaches performance of an infringing use. These cases make clear that the instructions in the label itself are sufficient for finding the requisite specific intent. *See In re Depomed Patent Litig.*, 2016 U.S. Dist. LEXIS 166077, at *181-82 (finding defendants possessed specific intent based on "the instructions in the label itself" and that "[i]nformation outside the label (e.g., a physician's knowledge) is not sufficient to meet the standard." (citation omitted)); *see also Sanofi v. Watson Laboratories Inc.*, 875 F.3d 636, 644-46 (Fed. Cir. 2017) (affirming verdict of inducing infringement where label encouraged patient to use drug in manner that infringed claims, relying on data of actual usage of drug product as further evidence that labeling encouraged infringement, and rejecting contention that

because drug had substantial noninfringing uses there could not be inducing infringement).

Here, the content of the ANDA labels virtually compels an inference of specific intent to encourage the infringing use, and I do draw that inference. Claim 1 of the '438 patent, the only independent claim, is a method of treating prostate cancer by the administration of abiraterone and prednisone. (JTX 8000). Dependent claims 2–20 of the '438 patent describe additional limitations of the method, including the amount of abiraterone acetate (1000mg/day) and the amount of prednisone (10mg/day) used, and the type of prostate cancer being treated (mCRPC). (*Id.*). All of the defendants' label Indications promote that exact use. *See Bone Care Int'l, L.L.C. v. Roxane Labs., Inc.*, 2012 U.S. Dist. LEXIS 80450, at *33 (D. Del. June 11, 2012) (finding induced infringement where defendants' proposed labels did not differ from plaintiff's labels "in any relevant way.").

Defendants cite cases in which intent was not inferred from the label's content, but in those cases the infringing use was no more than an option. In none of those cases did the generic defendant successfully interpose an ostrich defense to Indication and Dosing sections that directly instructed infringing use, as they do here.

In *Shire*, for example, the patent claimed a method of administering a certain drug orally, with food. 2014 U.S. Dist. LEXIS 85369 at *15. In contrast, defendants' ANDA labels stated that the drug could be taken with or without food. *Id.* Consistent with the label, physicians could, at their option, infringe or not infringe. The court held accordingly:

> The problem is that the statement that the medication may be taken with or without food cannot be reasonably understood to be an instruction to engage in an infringing use. As Defendants contend, it is indifferent to which option is selected. At most, it may be understood to permit an infringing use, but permission is different from encouragement. . . . [T]he proposed label does not contain any instruction to take the medication with food. Plaintiffs have failed to raise a material factual dispute over whether the

proposed label encourages infringement of method claims requiring administration with food.

Id. at *16.

Similarly, in *Acorda*, the patent taught that a drug be taken with food. 2011 U.S. Dist. LEXIS 102875, at *2. The proposed label directed physicians to "the pharmacokinetics section of the label for information on the differences between the fed and fasted states with capsules and tablets," and stated that physicians should be "thoroughly familiar with the complex effects of food" on the drug. *Id.* at *17. Finding that the labels did not infringe, the court explained that none of the label's statements "direct any action on the part of any physician, but merely call attention to the pharmacokinetics section." *Id.* In addition, the label did not state "a preference of one over the other or a direction to use the capsule form in the fed state." *Id.* Here, too, the options were "with food" or "without food," and the label did not promote one over the other.

The ANDA defendants' abiraterone labels are a far cry from that. The *only* way to follow these labels is to administer abiraterone, together with prednisone, in specified doses, to a mCRPC patient.[26]

I am also unpersuaded by defendants' argument that doctors will prescribe prednisone only for the unpatented purposes of palliation or minimizing side effects. First, this hypothetical possibility is contrary to the labels' explicit Indication, *i.e.*, abiraterone plus prednisone for the treatment of mCRPC. Second, this argument is best considered as a substantial non-infringing use under § 271(c), not as a rebuttal of intent under § 271(b). *See Sanofi*, 875 F.3d at 646 ("a person can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses") (citing *Grokster*, 545 U.S. at 934-37). Third, courts have found induced infringement

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[26] Nor is there persuasive evidence that the defendants took affirmative steps to avoid infringing uses, as in *Otsuka Pharm.*, 99 F. Supp. 3d at 485 ("The fact that . . . Defendants actively and voluntarily removed any reference to the allegedly infringing indication, in turn, belies any suggestion that these Defendants acted with the specific intention to encourage infringement.")

even in situations where a label did not track the patent's description of an underlying medical condition, but instead sought to treat a symptom. Infringement was found because the use of the product would entail the patented treatment of the underlying condition. *See, e.g., L.A. Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 2014 U.S. Dist. LEXIS 185431, at *13-14 (C.D. Cal. May 12, 2014) (noting that "a once daily dosage of [drug] to treat [symptom] in these patients results directly in treatment of the underlying [condition] and the performance of the patented method.").

Proposed labeling that instructs infringing uses is generally sufficient to support a finding of intentional inducement. The defendants' proposed labels here would infringe each element of the asserted claim. They teach the reader to perform every element of the patented method. With respect to the specific intent element, I conclude that the plaintiffs have sufficiently shown that the defendants "knew or should have known [their] actions would induce actual infringements." *See DSU Med. Corp.*, 471 F.3d at 1306. All defendants filed ANDAs seeking approval to market abiraterone under a label which instructs physicians and medical professionals to administer abiraterone plus prednisone in accordance with the patented method. This indication is the same use set forth in the patent-in-suit, and the labels of the defendants' proposed products are the same as the ZYTIGA® labels. *See* 21 C.F.R. § 314.94(a)(1)(8)(iv).

Accordingly, I find that plaintiffs have proven that, assuming the '438 patent is valid, the defendants would intentionally induce infringement if permitted to market their ANDA products under the proposed labels.

2. Contributory infringement

Plaintiffs also claim that abiraterone is a material part of a claimed invention, and that defendants are thus liable for contributory infringement (again, assuming that the '438 patent is valid). The parties give this claim very little attention in their briefing, and my finding of induced infringement renders it redundant. I therefore address it in abbreviated fashion.

Contributory infringement is prohibited by 35 U.S.C. § 271(c):

> Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

Stated simply, "[a] party is liable for contributory infringement if that party sells, or offers to sell, a material or apparatus for use in practicing a patented process." *i4i Ltd. P;ship v. Microsoft Corp.*, 598 F.3d 831, 850-51 (Fed. Cir. 2010). To establish contributory infringement under this subsection, a patent owner must prove the following: "1) that there is direct infringement, 2) that the accused infringer had knowledge of the patent, 3) that the component has no substantial noninfringing uses, and 4) that the component is a material part of the invention." *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326, 96 U.S.P.Q.2d 1742 (Fed. Cir. 2010).

Defendants concede, at least *arguendo,* elements 1, 2, and 4. The dispute focuses on the third element. Prednisone, say defendants, has a substantial non-infringing use as a glucocorticoid replacement. (DBr. at 32). "[D]istribution of a component of a patented device will not violate the patent if it is suitable for use in other ways." *Grokster*, 545 U.S. at 932. "[T]he doctrine absolves the equivocal conduct of selling an item with substantial lawful as well as unlawful uses." *Id.* A non-infringing use is substantial if it is "not unusual, far-fetched, illusory, impractical, 'occasional, aberrant, or experimental." *Vita-Mix Corp.*, 581 F.3d at 1327.

I find defendants' argument unpersuasive for several reasons. First, every administration of prednisone as a glucocorticoid replacement to treat mCRPC would factually duplicate the patented method. The noninfringing "use," then, is not so easily separated from the infringing one. This is not like using a patented anvil to moor a boat. The distinction between infringement

and noninfringement seems to turn, not on any external fact, but on the subjective mental processes of the prescribing physician.

Defendants' reliance on *Warner-Lambert* is therefore misplaced; that case involved an off-label use to treat a separate condition. As noted above, the patented method of treating neurodegenerative diseases was distinct from the FDA approval of the drug for "treatment of partial seizure" (which is not itself a neurogenerative disease). 316 F.3d at 1352. The court explained that "it defies common sense to expect that Apotex will actively promote the sale of its approved gabapentin, in contravention of FDA regulations, for a use that (a) might infringe Warner-Lambert's patent and (b) constitutes such a small fraction of total sales." *Id.* at 1365.

There, gabapentin was not approved by the FDA for the patented use in relation to a particular medical condition. Here, by contrast, the label-indicated use *is* the patented combination use. The prednisone does not know why it was administered, and its pharmacological effect when administered to a mCRPC patient with abiraterone will be the same, irrespective of any mental reservation by the physician. *Cf. L.A. Biomedical Research Inst.*, 2014 U.S. Dist. LEXIS 185431, at *13-14 (noting that "a once daily dosage of [drug] to treat [a symptom] in these patients results directly in treatment of the underlying [condition] and the performance of the patented method.").

Defendants argue in the alternative that Section 5.2 of their ANDA labels, the Warnings and Precautions Section, encourages abiraterone monotherapy. (DPF. at 63, ¶244). I look to the Indications. Abiraterone monotherapy is an off-label use, and there is no evidence in the record that this proposed off-label use is or would be "substantial." *Cf. Acorda Therapeutics*, 2011 WL 4074116 at **14, 19 (finding substantial non-infringing use where evidence showed that 75% of the sales of the product were for non-infringing use). If anything, the Warning section discourages such off-label use by suggests that withdrawing the use of prednisone from the combination therapy can have detrimental effects on a patient.

I therefore find that contributory infringement is present here as well.

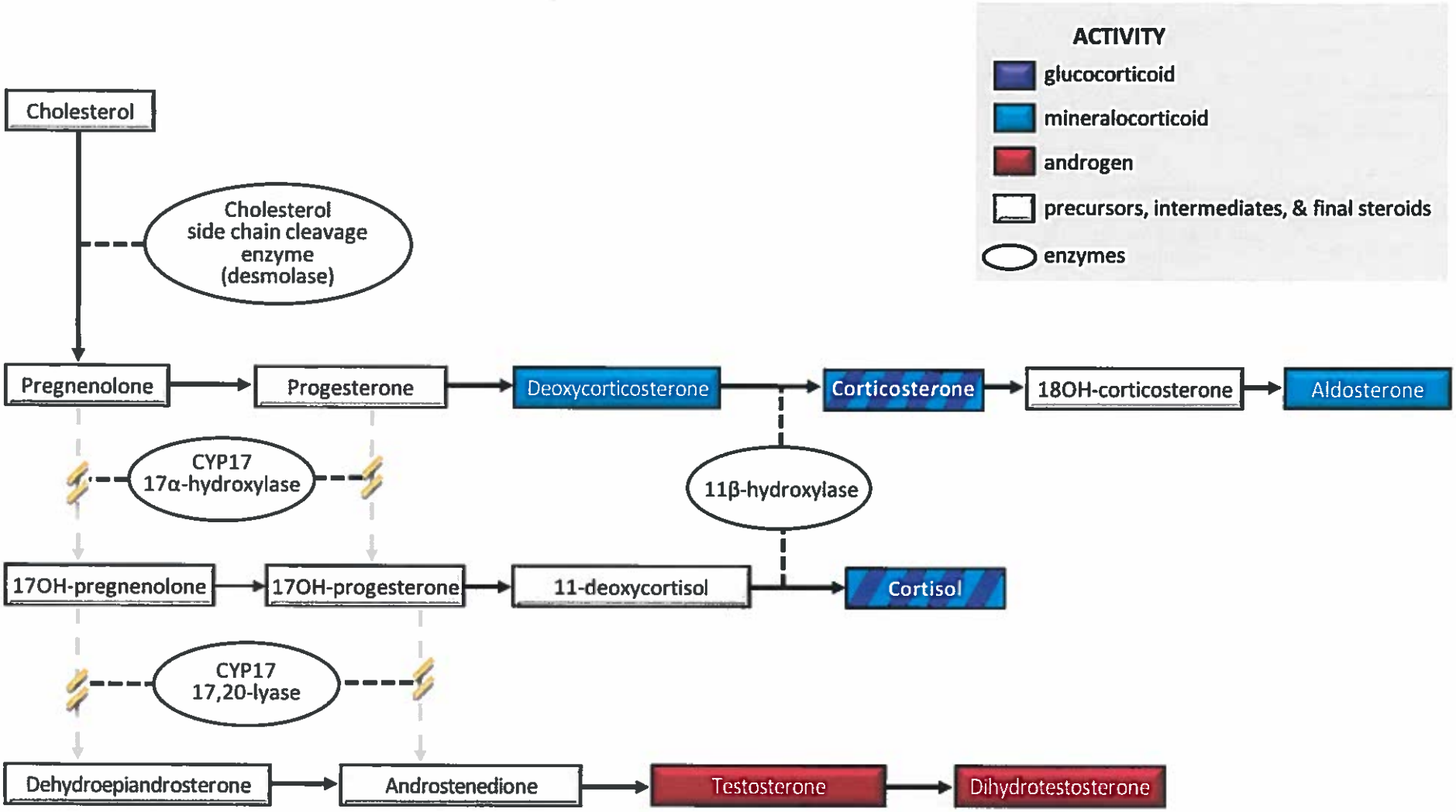
III. CONCLUSION

The '438 patent is invalid for obviousness, but contains an adequate written description. The plaintiffs have established by a preponderance of the evidence that if the patent were valid, defendants' activities would constitute induced infringement and contributory infringement.

Dated: October 25, 2018

KEVIN MCNULTY
United States District Judge

Abiraterone Acetate – Selective Inhibition



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